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ASCO SPECIAL ARTICLE

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

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ABSTRACT

Purpose
To provide evidence-based guidance on the optimum prevention and treatment approaches in the management of chemotherapy-induced peripheral neuropathies (CIPN) in adult cancer survivors.

Methods
A systematic literature search identified relevant, randomized controlled trials (RCTs) for the treatment of CIPN. Primary outcomes included incidence and severity of neuropathy as measured by neurophysiologic changes, patient-reported outcomes, and quality of life.

Results
A total of 48 RCTs met eligibility criteria and comprise the evidentiary basis for the recommendations. Trials tended to be small and heterogeneous, many with insufficient sample sizes to detect clinically important differences in outcomes. Primary outcomes varied across the trials, and in most cases, studies were not directly comparable because of different outcomes, measurements, and instruments used at different time points. The strength of the recommendations is based on the quality, amount, and consistency of the evidence and the balance between benefits and harms.

Recommendations:
On the basis of the paucity of high-quality, consistent evidence, there are no agents recommended for the prevention of CIPN. With regard to the treatment of existing CIPN, the best available data support a moderate recommendation for treatment with duloxetine. Although the CIPN trials are inconclusive regarding tricyclic antidepressants (such as nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine, these agents may be offered on the basis of data supporting their utility in other neuropathic pain conditions given the limited other CIPN treatment options. Further research on these agents is warranted.

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INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a common treatment-related adverse effect and affects long-term quality of life.[1] It has the potential to result in chemotherapy dose reductions and/or early discontinuation. The overall incidence of CIPN is estimated to be approximately 38% in patients treated with multiple agents,[2] although this percentage varies depending on chemotherapy regimens, duration of exposure, and assessment methods.[3,4] Chemotherapy combinations with higher incidences include those that involve platinum drugs, vinca alkaloids, bortezomib, and/or taxanes.[5] Although the pathogenesis and toxicity profiles of these agents differ, there are several distinguishing features of CIPN that help differentiate it from other neuropathies.[6] Classically, most chemotherapy drugs that cause CIPN do so with a symmetric, distal, length-dependent "glove and stocking" distribution. This neuropathy predominantly consists of sensory, rather than motor, symptoms and is dose dependent.[4,6] Sensory axonal damage with reduced amplitude of the sensory nerve action potentials (SNAPs) is a common finding in nerve conduction studies.[7] Conversely, motor nerve function consistently remains unchanged during treatment with most neurotoxic agents.[7] As chemotherapy is

THE BOTTOM LINE

GUIDELINE QUESTION

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

Target Population

- Adult cancer survivors with chemotherapy-induced neuropathies (CIPNs)

Target Audience

- Health care practitioners who provide care to cancer survivors

Recommendations

- The following recommendations are evidence based, informed by small randomized controlled trials, and guided by clinical experience. The recommendations were developed by a multidisciplinary group of experts. Ratings for benefits, harms, evidence quality, and recommendation strength are provided in Table 3 (see Appendix Table A1, online only, for rating definitions).

Prevention of CIPN

- There are no established agents recommended for the prevention of CIPN in patients with cancer undergoing treatment with neurotoxic agents. This is based on the paucity of high-quality, consistent evidence and a balance of benefits versus harms.
- Clinicians should not offer the following agents for the prevention of CIPN to patients with cancer undergoing treatment with neurotoxic agents:
- Acetyl-L-carnitine (ALC)
- Amifostine
- Amitriptyline
- CaMg for patients receiving oxaliplatin-based chemotherapy
- Diethyldithio-carbamate (DDTC)
- Glutathione (GSH) for patients receiving paclitaxel/carboplatin chemotherapy
- Nimodipine
- Org 2766
- All-*trans*-retinoic acid
- rhuLIF
- Vitamin E

  Venlafaxine is not recommended for routine use in clinical practice. Although the venlafaxine data support its potential utility, the data were not strong enough to recommend its use in clinical practice, until additional supporting data become available.

  No recommendations can be made on the use of *N*-acetylcysteine, carbamazepine, glutamate, GSH for patients receiving cisplatin or oxaliplatin-based chemotherapy, goshajinkigan (GJG), omega-3 fatty acids, or oxycarbazepine for the prevention of CIPN at this time.

Treatment of CIPN

- For patients with cancer experiencing CIPN, clinicians may offer duloxetine

  No recommendations can be made on the use of:
- ALC, noting that a positive phase III abstract supported its value, but this work has not yet been published in a peer-reviewed journal, and a prevention trial suggested that this agent was associated with worse outcomes.
- Tricyclic antidepressants; however, based on the limited options that are available for this prominent clinical problem and the demonstrated efficacy of these drugs for other neuropathic pain conditions, it is reasonable to try a tricyclic antidepressant (eg, nortriptyline or desipramine) in patients suffering from CIPN after a discussion with the patients about the limited scientific evidence for CIPN, potential harms, benefits, cost, and patient preferences.
- Gabapentin, noting that the available data were limited regarding its efficacy for treating CIPN. However, the panel felt that this agent is reasonable to try for selected patients with CIPN pain given that only a single negative randomized trial for this agent was completed, the established efficacy of gabapentin and pregabalin for other forms of neuropathic pain, and the limited CIPN treatment options. Patients should be informed about the limited scientific evidence for CIPN, potential harms, benefits, and costs.

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- A topical gel treatment containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg), noting that a single trial indicated that this product did decrease CIPN symptoms. Given the available data, the panel felt that this agent is reasonable to try for selected patients with CIPN pain. Patients should be informed about the limited scientific evidence for the treatment of CIPN, potential harms, benefits, and costs.

Note: The guide for rating recommendations and strength of evidence is provided in Appendix Table A1 (online only).

continued, symptoms get progressively worse, without improvement between doses. When cumulative oxaliplatin-induced peripheral neuropathy develops, it is reported to be partially reversible in approximately 80% of patients and completely resolves in approximately 40% at 6 to 8 months after cessation of treatment.[7] However, signs and symptoms may continue to develop and progress for an additional 2 to 6 months post-therapy, a phenomenon known as "coasting."[7] Paclitaxel peripheral neuropathy also improves in most patients in the months after cessation of treatment, but continues to be a prominent long-term problem in a subset of patients.[1,8,9]

Some neuropathy-inducing chemotherapy agents, such as taxanes and oxaliplatin, cause an acute neuropathy syndrome in addition to CIPN. Despite being a clinically distinct form and not necessarily being peripheral in distribution, this chemotherapy-induced acute neuropathy is addressed in this guideline. Oxaliplatin-induced acute neurotoxicity is characterized by a unique spectrum of acute motor and sensory symptoms occurring in the hours to days following infusion.[10-12] These symptoms include sensitivities to touching cold items, discomfort swallowing cold liquids, throat discomfort, and muscle cramps. Patients with more severe acute neuropathy appear to also be at an increased risk of experiencing more severe chronic peripheral neuropathy.[7,13] Paclitaxel-induced acute neuropathy consists of an acute pain syndrome, which usually develops within 1 to 3 days of paclitaxel administration and largely resolves within a week.[14] This pain complex had classically been labeled as a form of arthralgia/myalgia, but there are no good data to support that this pain syndrome arises from a pathologic process related to joints or muscles,[14,15] and detailed descriptive data support that this syndrome is likely a form of acute neuropathy.[14] This syndrome occurs in the majority of patients and is more prominent in patients receiving higher individual paclitaxel doses.[14,16]

Many of the agents chosen to undergo evaluation for the treatment and prevention of CIPN were agents with a record of efficacy for other common neuropathic pain conditions, such as painful diabetic peripheral neuropathy and postherpetic neuralgia. This has been done despite CIPN being relatively distinct from other forms of neuropathic pain in many ways, including pathophysiology and symptomatology.[17] The purpose of this systematic review and evidence-based guideline is to systematically review RCTs reported in the literature, compare outcomes among trials, and provide guidance on the effectiveness of prevention and treatment options for CIPN in adults with a history of cancer.

CLINICAL PRACTICE GUIDELINES

Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, utilization of clinical guidelines may provide:

1. Improvements in outcomes
2. Improvements in clinical practice
3. A means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for health professional orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where future research is needed

GUIDELINE QUESTION

What are the optimum prevention and treatment approaches in the prevention/management of CIPNs in adult cancer survivors?

METHODS

Panel Composition

To address the clinical question, an Expert Panel with multidisciplinary representation in medical oncology, community oncology, nursing, pain research, genetics, neurology, pharmacology, patient representation, and guideline methodology was convened. The Expert Panel was led by two Co-chairs who had the primary responsibility for the development and timely completion of the guideline. The Expert Panel members are listed in Appendix Table A2 (online only).

Guideline Development Process

The Expert Panel members, who met via teleconference and corresponded through e-mail:, were asked to contribute to the development of the guideline, provide critical review, interpret evidence, and finalize the guideline recommendations based on consideration of the evidence. Members of the Expert Panel were responsible for drafting the penultimate version of the guideline, which was then circulated for external review. All ASCO guidelines

are reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication.

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 therein should not be relied on 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" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating clinician 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, expressed 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 Conflict of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines (Procedures; summarized at http://www.asco.org/guidelinescoi). Members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Panel did not disclose any such relationships.

Systematic Literature Review

ASCO guidelines are based on systematic reviews. A protocol for each guideline defines the parameters for a targeted literature search including relevant study designs, literature sources, types of reports, and prespecified study selection criteria for literature identified.

Literature Search Strategy

Ovid MEDLINE (1946 to April week 2, 2013), EMBASE (1980 to 2013 week 16), and AMED (Allied and Complementary Medicine; 1985 to April 2013) databases were searched for evidence reporting on outcomes of interest. Before the systematic search of the medical literature, an environmental scan was conducted for existing reviews regarding the management of CIPN. With no recent guidelines identified, older reviews with contents related to the clinical questions had their included studies cross-referenced to our literature search. Reference lists from other published seminal papers were scanned for additional citations. The literature search strategy and search results are available in Appendix Table A3 (online only) and Appendix Figure A1, (online only), respectively.

Study Selection Criteria

Articles were selected for inclusion in the systematic review of the evidence if they

- focused on chemotherapy-induced neuropathy
- included cancer survivors
- considered neuropathy as an important outcome of study
- were randomized trials (phase II and III)

Articles were excluded from the systematic review if they

- were phase I studies, other noncomparative studies, case reports, editorial letters, or newspaper articles
- only involved individuals under 18 years of age
- were animal studies
- were published in a language other than English
- included less than 10 participants
- focused on radiation therapy related neuropathy or stem-cell transplantation–related neuropathy

Outcomes of Interest

The outcomes of interest included incidence and severity of neuropathy, neurophysiologic changes, symptom relief, patient-reported outcomes (PROs), and quality of life.

Data Extraction

Literature search results were reviewed and deemed appropriate for full-text review by an ASCO staff member in consultation with the Co-Chairs. Data were extracted in duplicate by two ASCO staff members. Disagreements were resolved through discussion and consultation with the Co-Chairs, if necessary.

Revision Dates

The Co-Chairs determine the need for guideline updates or revisions based on periodic review and consideration of the literature. If new and compelling data are identified, the Expert Panel or an Update Committee is reconvened to discuss revisions to the document.

RESULTS

The literature search identified 1,252 potentially relevant citations. Of these, 250 were examined in detail, and a total of 48 RCTs ultimately met eligibility criteria and comprise the evidentiary basis for the guideline recommendations. A summary of the literature search results is provided in a QUOROM diagram in Appendix Figure A1.

The identified trials spanned a 23-year period, from 1990 to 2013. A total of 42 studies covered 19 different interventions for the prevention of CIPN. Treatment of established CIPN was considered in six RCTs investigating six different agents.

STUDY QUALITY

Study quality was formally assessed for the 48 identified RCTs (Table 1). Design aspects related to the individual study quality were assessed by one reviewer for factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on. The risk of bias was assessed as low to moderate for most of the identified trials, although five trials did suffer from various methodological shortcomings and were assessed to be at a high risk for bias. Overall, the trials tended to be small, with many having insufficient sample sizes to detect differences in outcomes. Dropout rates were also substantial in several trials. Several other factors related to increased potential for bias for the overall body of evidence were also recorded. Five of the trials were reported as phase II studies,[18-22] six were reported as pilot trials,[23-28] six were terminated early[11,19,29-32] and five were open label.[22,28,33-35] Primary outcomes varied across the trials, and, in the majority of cases, studies were not directly comparable because of different outcomes, measurements, and instruments used at different time points. Appendix Table A4 (online only) provides definitions of ratings for overall potential risk of bias.

Table 1. Quality Assessment

Study	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-Up	Intention-to-Treat Analysis	Insignificant COIs	Overall Potential Risk of Bias*
Prevention										
Lin 2006[23]	?	?	?	—	?	√	√	?	?	Intermediate
Hershman 2013[57]	√	?	√	√	√	√	√	?	√	Low
Kemp 1996[37]	√	?	√	√	?	√	√	√	?	Low
Planting 1999[39]	?	?	√	√	?	√	√	?	?	Intermediate
Lorusso 2003[38]	√	√	√	√	?	?	√	√	?	Low
Kanat 2003[36]	√	?	?	√	?	√	√	?	?	Intermediate
Leong 2003[40]	√	√	—	√	√	√	√	?	?	Low
Hilpert 2005[18]	√	?	√	?	√	√	√	?	?	Low
Kautio 2009[41]	√	√	—	√	√	√	√	√	?	Low
Ishibashi 2010[30]	√	√	—	√	√	√	√	?	√	Low
Chay 2010[19]	√	√	—	√	√	√	√	√	—	Low
Grothey 2008[Abst 32]	√	?	—	?	√	√	—	?	?	Unknown†
Grothey 2011[11]	√	√	—	√	√	√	—	√	√	Low
Von Delius 2007[20]	√	√	—	√	√	√	√	√	√	Low
Gandara 1995[60]	√	?	—	√	√	√	√	?	?	Intermediate
Loprinzi 2013[44]	√	√	√	√	√	√	√	?	?	Low
Loven 2009[24]	√	√	—	?	√	√	√	—	?	Intermediate
Wang 2007[28]	√	—	√	√	—	√	√	?	√	High
Bogliun 1996[25]	√	?	?	√	√	√	√	?	?	Intermediate
Cascinu 1995[48]	√	√	√	√	√	√	√	?	?	Low
Cascinu 2002[47]	√	√	√	√	√	√	√	√	?	Low
Milla 2009[49]	?	?	?	?	?	√	√	?	?	Intermediate
Schmidinger 2000[26]	?	?	—	√	?	√	√	√	?	Intermediate
Smyth 1997[50]	√	√	?	√	√	√	√	?	?	Low
Leal 2013[51]	√	√	√	√	√	√	√	?	?	Low
Nishioka 2011[34]	√	√	√	√	—	√	√	?	√	Low
Cassidy 1998[31]	√	√	—	√	√	—	—	?	?	High
Ghoreishi 2012[58]	√	√	√	√	√	√	—	?	√	Low
Van der Hoop 1990[53]	√	√	?	√	√	√	√	?	?	Low
Van Kooten 1992[27]	√	?	?	—	√	√	√	?	?	Intermediate
Roberts 1997[54]	√	?	√	√	√	√	√	?	?	Low
Hovestadt 1992[55]	?	?	—	?	√	√	√	?	?	Intermediate
Van Gerven 1994[56]	?	?	?	√	√	√	√	—	?	Intermediate
Koeppen 2004[52]	√	?	?	√	√	√	√	?	?	Intermediate
Argyriou 2006a[35]	√	√	?	√	—	√	√	√	√	Intermediate
Arrieta 2011[59]	√	?	?	√	√	√	?	?	√	Intermediate
Davis 2005[21]	√	√	√	?	√	√	√	√	?	Low
Durand 2012[29]	√	?	—	√	√	√	?	?	√	Intermediate
Kottschade 2011[45]	√	√	—	√	√	√	√	?	√	Low
Argyriou 2006b[22]	√	?	?	√	—	√	√	√	√	High
Pace 2003[33]	?	?	?	√	—	—	√	—	?	High
Pace 2010[46]	√	√	√	√	√	√	√	?	?	High
Treatment										
Smith 2013[62]	√	?	√	√	√	√	√	?	√	Low
Rao 2007[64]	√	?	√	√	√	√	√	?	?	Low
Rao 2008[63]	√	?	√	√	√	√	√	?	?	Low
Hammack 2002[65]	√	?	√	√	√	√	√	?	√	Low
Kautio 2008[66]	√	√	—	√	√	√	√	√	?	Low
Barton 2011[67]	√	?	√	√	?	√	√	√	?	Low

NOTE. √ indicates criteria were met; — indicates criteria were not met; ? indicates insufficient detail, not reported, and/or uncertain if the criteria were met.
Abbreviation: COI, conflict of interest.
*Ratings are based on the estimation of whether the criterion was met and the extent of potential bias, not simply on reporting.
†Insufficient details provided in abstract to assess quality.

PREVENTION

Trial Results

A total of 42 RCTs were identified (Table 2) that studied the efficacy of pharmacologic agents, including anticonvulsants, antidepressants, vitamins, minerals, and other chemoprotectants in the prevention of CIPN.

Chemoprotectants. Six trials examined the efficacy of amifostine in the prevention of peripheral neuropathy associated with taxane-based chemotherapy regimens.[18,36-40] While there was evidence of the protective effect of amifostine against the incidence of neurotoxicity[18,36] and its severity,[18,37,38] this benefit was limited and not consistent across all studies. In addition, the limited benefit was counterbalanced by toxicities such as nausea, vomiting, and light-headedness.

A phase II trial[21] randomly assigned 117 patients with solid tumors receiving treatment with carboplatin/paclitaxel to low-dose (2 μg/kg) or high-dose (4 μg/kg) recombinant human leukemia inhibitory factor (rhuLIF) or placebo. This study was convincingly negative, with no differences between the groups in standardized composite peripheral nerve electrophysiology (CPNE) scores, the primary end point, or other secondary neurological testing variables considered.

A randomized placebo-controlled trial of the calcium-channel antagonist, nimodipine, was initiated in 51 patients with ovarian cancer.[31] As a result of an increase in nausea and vomiting and subsequent poor compliance, the trial was prematurely discontinued. Despite such early cessation, neurotoxicity scores were available for 40 patients, and results show an unexpected significant increase in scores for patients on nimodipine versus placebo ($P < .001$). This trial, despite its limitations, provides evidence that nimodipine can exacerbate neurotoxicity in patients receiving cisplatin-based regimens.

Anticonvulsants. Two trials assessed the effectiveness of anticonvulsants in the prevention of oxaliplatin-related neurotoxicity. A trial of carbamazepine was conducted in 36 patients with advanced colorectal cancer.[20] No significant difference in neurotoxicity was seen with carbamazepine compared with placebo, although this study was reported to be underpowered. Another randomized, open-label, controlled trial assessed the efficacy of oxcarbazepine for prophylaxis against oxaliplatin-induced peripheral neuropathy in 32 patients with colon cancer.[35] There was a 58% reduction in risk of CIPN in patients receiving oxcarbazepine compared with controls (risk ratio = 0.42; 95% CI, 0.19 to 0.91). Despite the positive results, the efficacy of oxcarbazepine in the prevention of CIPN remains uncertain. The trial had several limitations, including a small sample size and lack of a placebo control. Moreover, the clinical significance of the observed neurophysiologic outcome differences is unclear.

Antidepressants. Two trials[29,41] investigated the effects of antidepressants on peripheral neuropathy outcomes in patients with cancer. Kautio et al[41] found no difference in the amount of CIPN between patients receiving amitriptyline and those receiving placebo. In contrast, in a relatively small trial, the antidepressant venlafaxine was reported to significantly decrease oxaliplatin-associated acute neurotoxicity (31% *v* 5%, $P = .03$) and chronic peripheral neuropathy (supported by significantly fewer patients having grade 3 toxicity [0% *v* 33%, $P = .03$] in the venlafaxine arm), when compared with placebo.[29]

Vitamins, minerals, dietary supplements. A number of placebo-controlled trials examined the effect of calcium and magnesium (CaMg) infusions on oxaliplatin-induced neuropathy in patients receiving infusional fluorouracil, leucovorin, and oxaliplatin chemotherapy. This work was based on a nonrandomized trial that retrospectively compared its results to those from a historical population of patients, reporting that CaMg infusions were associated with a marked reduction of neuropathy[42]; this led to the subsequent relatively widespread adoption of this practice into routine clinical care. This led to the development of placebo-controlled trials, but many of these trials were terminated prematurely, based on an errant report from one study that associated less antitumor activity in patients receiving CaMg.[43] Three of these prematurely closed trials did not show any significant neuropathy benefit from CaMg[19,30,32] while one reported a significant decrease in the incidence of chronic, cumulative, grade ≥ 2 sensory neuropathy, as measured by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; $P = .038$) and the oxaliplatin-specific sensory neurotoxicity scale ($P = .018$).[11] Recently, a large double-blind randomized trial of 353 patients with colon cancer provided strong evidence that CaMg was not able to significantly decrease either the acute or persistent neuropathy associated with oxaliplatin.[44]

Four trials of varying methodological quality evaluated the neuroprotective effect of antioxidant supplementation with vitamin E in patients treated with taxanes or platinum-based regimens.[22,33,45,46] Although the first three published trials[22,33,46] provided data to support that vitamin E could decrease neuropathy, two of these trials[22,33] were relatively small, and both used an open-label control group without a placebo. The third trial[46] randomly allocated 108 patients receiving cisplatin therapy to vitamin E or placebo. However, only 41 of these patients qualified for inclusion in the statistical analysis. Although this trial reported that the vitamin E group appeared to have less neuropathy than those receiving placebo, only 17 patients randomly allocated to vitamin E were considered in the analysis. The limited number of subjects included in the analysis is inadequate to demonstrate vitamin E's neuroprotective effects against cisplatin-induced neuropathy. The largest, most recently published trial involved 207 patients and reported that vitamin E did not appear to reduce the incidence of sensory neuropathy.[45]

Six small randomized trials[25,26,47-50] evaluated the protective effects of glutathione (GSH) against platinum-based neurotoxicity. Five of these trials[25,47-50] reported a statistically significant reduction in neurotoxicity, in one form or another, with administration of GSH compared with placebo. Benefits included a reduction in incidence and severity of neuropathy and improvements in nerve conduction and QOL. In addition, a small, randomized, placebo-controlled pilot study of *N*-acetylcysteine, an antioxidant known to increase serum glutathione concentrations, was conducted in 14 patients with stage III colon cancer receiving oxaliplatin-based adjuvant chemotherapy.[23] This study reported that grade 2 to 4 sensory neuropathy was lower in the treatment arm (20%) compared with the placebo arm (73%) after 12 cycles of chemotherapy ($P < .05$). In contrast to the above data suggesting that GSH is beneficial, a recent larger placebo-controlled trial was unable to provide data supporting the benefit of GSH for the prevention of neurotoxicity in 185 patients receiving paclitaxel/carboplatin therapy.[51] As carboplatin is the least neurotoxic of the platinum agents, it appears that most of the neuropathy from this regimen was dictated by paclitaxel. Thus, the results of this study suggest that GSH is not an effective agent in the prevention of taxane-induced CIPN. It

Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
Acetylcysteine (NAC)	Lin 2006[23]	Platinum	14 total; NAC: 5, PL: 9	1,200 mg orally	*Clinical grade 1 after 4 cycles, assessed by NCI-CTC classification**: NAC: 40%, PL: 77.8%; $P = .158$	*Grade 2-4 after 8 cycles assessed by NCI-CTC classification**: NAC: 0%, PL: 56%; $P < .05$ *Grade 2-4 after 12 cycles assessed by NCI-CTC classification**: NAC: 20%, PL: 89%; $P < .05$	No significant changes in mean latency, sensory amplitude potentials, or conduction velocity of sural nerves in patients receiving NAC†	NR
Acetyl-L-carnitine (ALC)	Hershman 2013[57]	Taxane	409 total; ALC: 208, PL: 201	3,000 mg/day	NR	*FACT-NTX score‡ 12-wk (mean)**: ALC: 35.4, PL: 36.4; $P = .17$ *FACT-NTX score‡ 24 wk (mean)†:* ALC: 35.3, PL: 37.5; $P = .01$ NR	*FACT-TOI score‡ 12-wk (mean)†:* ALC: 91.9, PL: 92.5; $P = .92$ *FACT-TOI score‡ 24 wk (mean)†:* ALC: 95.1, PL: 98.9; $P = .03$ *FACT-Fatigue score‡ 12 wk (mean)†*: ALC: 36.4, PL: 35.5; $P = .2$ *FACT-Fatigue score‡ 24 wk (mean)†*: ALC: 39.3, PL: 40.3; $P = .51$	
Amifostine (AM)	Kemp 1996[37] *Note: CIPN not primary outcome*	Platinum	242 total; AM: 122, PL: 120	Amifostine was reconstituted with 9.5 mL normal saline, and the dose of 910 mg/m^2 was administered as a 15-min intravenous infusion	NR	*Severity of neuropathy after 6 cycles assessed by NCI-CTC classification:* grade 1: AM: 29%, PL: 31%; grade 2*:* AM: 29%, PL: 35%; grade 3: AM: 9%, PL: 15%; $P = .029$	NR	NR
	Planting 1999[39] *Note: CIPN not primary outcome*	Platinum	73 total; AM: 36, PL: 37	740 mg/m^2 over a 15-min infusion directly before cisplatin was given	*Grade 1 neuropathy assessed by NCI-CTC classification:* AM: 28.6%, PL: 25%; $P =$ NR	NR	Serial vibration perception thresholds (VPT) showed a diminished incidence of subclinical neurotoxicity in the amifostine arm ($P = .03$)	NR
	Lorusso 2003[38] *Note: CIPN not primary outcome*	Carboplatin/paclitaxel	187 total; AM: 93, PL: 94	910 mg/m^2 given as a 15-min infusion, administered directly before paclitaxel administration	NR	*Grade 3-4 neurotoxicity assessed by NCI-CTC classification:* AM: 3.7% (95% CI, 2.1 to 5.3) PL: 7.2% (95% CI, 5.0 to 9.4) $P = .021$	NR	NR

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
	Kanat 2003[36] *Note: CIPN not primary outcome*	Carboplatin/paclitaxel	38 total; AM: 19, PL: 19	910 mg/m^2 given as a 15-min infusion, administered within 30 min preceding carboplatin infusion	*Grade 1-2 paresthesia assessed by NCI-CTC classification:* AM: 42.1%, PL: 94.7%; $P = .018$	NR	Mean SNAP amplitudes were comparable after 6 cycles of chemotherapy, and there was no significant decline in mean amps for either group after treatment	NR
	Leong 2003[40] *Note: CIPN not primary outcome*	Carboplatin/paclitaxel	60 total; AM: 30, PL: 30	740 mg/m^2 over a 15-min infusion 30 mins before paclitaxel and 30 mins before to carboplatin	*Grade 2-3 neuropathy assessed by NCI-CTC classification:* AM: 24%, PL: 37%; P = NR	NR	Overall, the 72 neurophysiologic parameters before and after treatment showed worsening in both treatment groups, but there was no statistical difference between groups	NR
	Hilpert 2005[18]	Carboplatin/paclitaxel	72 total; AM: 37, PL: 34	740 mg/m^2 over a 15-min infusion 30 mins prior to chemo	CTCAE scores were better with AM ($P = .01$)		*Maximum VPT hands*:* AM: 3.18 μm (after 5 cycles), PL: 3.83 μm (after 6 cycles); $P = .0114$ (by multivariable analysis) *Maximum VPT feet*:* AM: 5.25 μm (after 6 cycles) PL: 11.88 μm (after 3 mo follow up) $P = .0015$ (by multivariable analysis) *Maximum VDT hands*:* AM: 2.75 μm (after 6 cycles), PL: 2.93 μm (at 3 mo follow- up) $P = .0038$ (by multivariable analysis) *Maximum VDT feet*:* AM: 5.42 μm (after 6 cycles), PL: 8.61 μm (after 6 cycles); $P = .0012$ (by multivariable analysis)	*EORTC-QLQ-C-30 Global health status score trend over treatment period†:* AM: $P = .0026$; PL: $P = .4478$ *EORTC-QLQ-C-30 Global health status score trend over follow up period†:* AM: $P = .0098$ PL: $P = .3740$
Amitriptyline (AMI)	Kautio 2009[41]	Vinca alcaloids, platinum or Taxanes	114 total; AM: 58, PL: 56	25 mg/d up to maximum of 100 mg/d until end of neurotoxic chemotherapy	No significant difference in appearance or progression of neuropathic symptoms based on diary data between groups*.	*NCI-CTC grading on visits 4†:* Any sensory: AMI: 61%, PL: 76%; P = NS Grade 3 motor AMI: 26%, PL: 22%; P = NS	NR	*EORTC-C30†:* no significant difference between groups

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
Calcium and magnesium (Ca/Mg)	Ishibashi 2010[30]	Oxaliplatin	33 total; Ca/Mg: 17, PL: 16	Calcium gluconate 850 mg and magnesium sulfate 720 mg	*DEB-NTS and NCI-CTC criteria for ≥ grade 1*:* Ca/Mg: 100%, PL: 94%; $P = .48$	*DEB-NTS criteria for ≥ grades 2 and 3*:* Ca/Mg grade 2: 71%, PL grade 2: 56%; $P = .48$ Ca/Mg grade 3: 6% PL grade 3: 0% $P > .99$ *NCI-CTC Criteria for ≥ grade 2*:* Ca/Mg: 6% PL: 6%; $P > .99$	NR	NR
	Chay 2010§[19]	Oxaliplatin	27 total enrolled (8 did not complete study as a result of study termination); CaMg: 9, PL: 10	Calcium gluconate 1g and 15% magnesium sulfate 1 g diluted into 100 mL of saline infused before and after chemotherapy	NR	*Grade 1-2 numbness assessed by NCI-CTC classification:* CaMg: 44%, PL: 70%; P = NR *Grade 3 OSS or CTC numbness:* CaMg: 11%, PL: 0%; $P = .09$	*Objective neuropathy score at end of treatment assessed by NCS:* CaMg: 6, PL: 0; $P = .02$ (note: higher scores = worse neuropathy)	*Acute subjective neuropathy:* CaMg: 77%, PL: 86%; $P = .6$
	Grothey 2011[11]	Oxaliplatin	102 total; CaMg: 50, PL: 52	Intravenous calcium gluconate plus magnesium sulfate, 1 g of each agent in 100 mL D5W over 30 min, immediately before and after each dose of oxaliplatin	*Incidence of ≥ grade 2 sensory neurotoxicity by NCI CTCAE classification*:* CaMg: 22%, PL: 41%; $P = .038$ *By OSS†:* CaMg: 28%, PL: 51%; $P = .018$	NR	NR	*Sensitivities to touching cold items, discomfort swallowing cold liquids, or throat discomfort†* No difference between CaMg and placebo arms *Muscle cramps at cycle 1 (AUC)†:* CaMg: 8 ± 20, PL: 46 ± 101; $P = .01$
	Grothey 2008[32] Abstract	Oxaliplatin	139 total; CaMg: NR, PL: NR	Ca-gluconate 1 g, Mg-sulfate 1 g, pre and post oxaliplatin	NR	No difference in time to treatment discontinuation with CaMg versus PL*: HR = 1.32 (95% CI, 0.93 to 1.86); $P = .1179$	NR	NR
	Loprinzi 2013[44]	Oxaliplatin	353 total; CaMg/CaMg: 118, CaMg/PL: 116, PL/PL: 119	1 g of each agent in 100 mL D5W over 30 min, immediately before and after each dose of oxaliplatin OR Ca-gluconate 1g, Mg-sulfate 1g, before and PL after oxaliplatin	NR	*CTCAE grade ≥ 2 neurotoxicity†:* CaMg/CaMg: 43%, CaMg/PL: 46%, PL/PL: 45%; no significant difference *EORTC CIPN-20 sensory*, motor†, or autonomic scales†:* no significant difference	NR	*Patient-reported acute neuropathy†:* no significant difference in sensitivities to touching cold, discomfort swallowing cold liquids, or muscle cramps but a decrease of throat discomfort with CaMg was reported ($P < .036$)

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
Carbamazepine (Carb)	Von Delius 2007[20]	Oxaliplatin	36 total; Carb: 19 PL: 17	200 mg and stepwise elevated by 200 mg until target plasma levels reached: 4-6 mg/L	*PNP numbness scores (worst grade, any cycle)†* : Carb: 5.3%, PL: 11.8%; $P = .2$	*Grade 3-4 according to Levi's scale*:* Carb: 21%, PL: 35%; $P = .72$	NR	NR
Diethyldithio-carbamate (DDTC)	Gandara 1995[60] *Note: neuropathy was not the only focus of study*	Platinum	214 total; DDTC: 106, PL: 108	1.6 g/m^2 over 4 h starting 15 min before cisplatin administration	*Clinical peripheral neuropathy:* DDTC: 13%, PL: 12%; $P =$ NS	NR	NR	Patients on active treatment had significantly more toxicity and were more likely to stop chemotherapy due to toxicity (9% *v* 23%, $P = .08$) and have a lower cumulative cisplatin doses ($P < .001$)
Glutamate/ Glutamine (Gluta)	Loven 2009[24]	Paclitaxel	43 total; Gluta: 23, PL: 20	500 mg, 3× per day	NR	*Severity of signs and symptoms rank at a severity score of 2 or 3*: Reduced touch perception:* Gluta: 0%, PL: 5.5%; $P = .47$ *Reduced pain perception:* Gluta: 0%, PL: 5.5%; $P = .47$ *Impaired deep sensation:* Gluta: 10%, PL: 22.2%; $P = .395$ *Impaired tendon reflexes:* Gluta: 20% PL: 16.7% $P = 1.0$	*Neuropathy as measured by electro-diagnostic abnormalities:* Gluta: 30.4%, PL: 30%	NR
	Wang 2007§[28]	Oxaliplatin	86 total; Gluta: 42, PL: 44	15g 2×/d for 7 d every 2 wk starting on the day of chemotherapy	*Grade 1-2 sensory neuropathy after 2 cycles assessed by NCI-CTC classification::* Gluta: 16.7%, PL: 38.6%; $P = .04$ *Grade 1-2 sensory neuropathy after 4 cycles assessed by NCI-CTC classification:* Gluta: 26.2%, PL: 36.4%; $P = .05$	NR	Abnormal electro-physiological exam: Gluta: 21.4%, PL: 25.0%; $P = .68$	*Interference with activities of daily living:* Gluta: 16.7%, PL: 40.9%; $P = .02$ *Presence of acute, cold-induced neurotoxicity:* Gluta: 33.3%, PL: 56.8%; $P = .03$

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
Glutathione (GSH)	Bogliun 1996§[25]	Cisplatin	54 total; GSH: 27, PL: 27	2.5g over 15 min, immediately before cisplatin	NR	*Change of >12 points in NDS:* GSH: 26.3%, PL: 50%; RR‖: 0.53 (95% CI, 0.21 to 1.29); $P = .16$	*Decrease in SNAP amplitude:* GSH: 12%–35%, PL: 58%–68% (depending on dose of CDDP); RR‖: 0.75 (95% CI, 0.56 to 0.99); $P = .043$	NR
	Cascinu 1995[48]	Cisplatin	50 total; GSH: 25 PL: 25,	1500 mg/m^2 GSH in 100 mL of saline over a 15-min period immediately before each CDDP administration and 600 mg by intramuscular injection on days 2 to 5	*Neurotoxicity assessed by WHO criteria*: After 9 wk of treatment:* GSH: 0%, PL: 66% (95% CI, 49% to 83%); $P < .001$ *After 15 wk of treatment:* GSH: 17% (95% CI, 2% to 32%), PL: 88% (95% CI, 76% to 100%); $P < .001$	NR	*Mean latency and SAPs†:* GSH: No changes of the median, ulnar, and sural nerves PL: mean SAPs were significantly affected at the 9th ($P \leq .003$) and 15th week ($P \leq .003$), and latency at the 15th week ($P \leq .01$)	NR
	Cascinu 2002[47]	Oxaliplatin	52 total GSH: 26 PL: 26	1500 mg/m^2 GSH in 100 mL of saline over a 15-min period immediately before each oxaliplatin administration	*Grade 1-2 neuropathy after 4 cycles assessed by NCI-CTC classification†:* GSH:27% (95% CI, 9.8-44%) PL: 42% (95% CI, 23-61%), P = NR *Any neuropathy after 8 cycles assessed by NCI-CTC classification:†:* GSH: 43% (95% CI, 22 to 64%), PL: 79% (95% CI, 60 to 80%); $P = .04$	*Grade 2-4 NCI CTC clinical neurotoxicity*:* GSH: 9.5% (95% CI, 0 to 22%), PL: 58% (95% CI, 35 to 80%) $P = .003$ *Grade 3-4 neurotoxicity†:* GSH: 0%, PL: 26%; $P = .01$	*Neurophysiologic evaluation after 8 cycles†:* GSH: no changes in mean latency and sensory amplitude potentials of the sural nerves PL: statistically significant change in mean latency ($P = .03$) and sensory amplitude ($P = .05$) potentials of the sural nerves	NR
	Leal 2013[51]	Paclitaxel/carboplatin	185 total; GSH: 94, PL: 91	1.5g/m^2 GSH IV over 15 min immediately before chemotherapy administration	*PN assessed by EORTC- QLQ-CIPN20*: $P = .21$*	*CTCAE grade ≥ 2 neurotoxicity†:* GSH: 38%, PL: 33% $P = .449$	NR	*Acute paclitaxel neuropathy†:* no significant advantage for glutathione ($P = .30$ for every 3 wk subset; $P = .002$ for the weekly subset, in favor of placebo arm)

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
	Milla 2009§[49]	Oxaliplatin	27 total; GSH: 14, PL: 13	1,500 mg/m^2 GSH in 100 mL of physiological saline over a 15-min period immediately before each oxaliplatin administration	*End of treatment neuropathy assessed by NCI-CTC classification:* GSH: grade 1: 50%, grade 2: 50%, grade 3: 0, grade 4: 0; PL: grade 1: 26%, grade 2: 69%, grade 3: 31%, grade 4: 0; $P = .0037$	NR	NR	NR
	Schmidinger 2000§[26]	Cisplatin	20 total; GSH: 11, PL: 9	5 g immediately before cisplatin	*WHO neurotoxicity measure:* No change in the GSH or PL group	NR	No significant difference in nerve conduction studies between the GSH and PL groups	NR
	Smyth 1997§[50]	Cisplatin	151 total GSH: 74 PL: 77	3 g/m^2 GSH infused over 20 min immediately before 100 mg/m^2 cisplatin every 3 weeks for six courses	*Neurosensory toxicity assessed by NCI-CTC classification:* GSH: 39%, PL: 49%; $P = .22$	NR	NR	*Rotterdam Symptom Checklist:* Peripheral neurotoxicity was significantly improved in the GSH group compared to the PL group ($P < .05$). *Proportion of patients receiving a full 6 courses at any dose:* GSH: 58%, PL: 39%; $P = .04$
Goshajinkigan (GJG) - Kampo medicine	Nishioka 2011[34]	Oxaliplatin	45 total; GJG: 22, unblinded control group: 23	7.5 g/d divided into 2-3 doses administered during chemotherapy	*Grade 3 assessed by DEB-NTC* after 10 courses:* GJG: 0%, unblinded control group: 12%; $P < .01$ *After 20 courses:* GJG: 33%, unblinded control group: 75%; $P < .01$	NR	NR	NR
Nimodipine (Nim)	Cassidy 1998[31]	Cisplatin	51 total (50 took study drug) Nim: 24, PL: 26	90 mg qds, but dose reduction in some patients occurred in an attempt to salvage poor compliance	NR	NR	NR	*Neurotoxicity Score at week 27 as measured by author-designed questionnaire*:* Nim: 10.4 ± 1.0, PL: 6.4 ± 0.8; $P < .001$

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
Omega 3	Ghoreishi 2012[58]	Paclitaxel	57 total; Omega: 30, PL: 27	640 mg (54% DHA, 10% EPA) 3×/d	A significant difference in PN incidence assessed by $rTNS^P$ OR = 0.3 (95% CI,0.10 to 0.88); $P = .029$	Borderline significant difference in severity of PN assessed by $rTNS^P$ B = −1.02 (95% CI, −2.06 to 0.02); $P = .054$ Ordinal regression analysis was used to compare the severity	*Sural a-SAP difference pre and post chemotherapy†:* Omega: +0.06 PL: −3.96 $P = .015$ Other differences of NCS parameters did not reach statistical significance†	NR
Org 2766	Van der Hoop 1990[53]	Cisplatin	55 total Org low 0.25 mg: 17 Org high 1 mg: 16 PL: 22	Two subcutaneous injections of either a 0.25 mg or 1 mg dose	NR	NR	*Threshold of vibration perception as measured with vibrameter after 4 cycles*:* PL: 1.61 ± 0.43, low: 0.56 ± 0.11 high: 0.50 ± 0.06; $P <$ .005 for high dose compared with placebo *Threshold of vibration perception as measured with vibrameter after 6 cycles†:* PL: 5.87 ± 1.97 low: 2.31 ± 0.75 high: 0.88 ± 0.17; $P <$ .005 for high dose compared with placebo	*Patient reported paresthesias after 4 courses†:* PL: 38% low: 8% high: 8%; $P = .16$ *After 6 courses†:* PL: 67%, low: 33%, high: 29%; $P =$ NR *Sum scores for patient-reported signs and symptoms after 4 courses†:* PL: 4.85, low: 3.69, high: 3.23; $P = .03$ *Sum scores for patient reported signs and symptoms after 6 courses†:* PL: 7.42, low: 4.33, high: 3.57; $P = .03$
	Roberts 1997[54]	Cisplatin	196 total; Org 2 mg: 63, Org 4 mg: 66, PL: 67	Two subcutaneous injections of either a 2-mg or 4-mg dose	NR	NR	*VPT* index finger (lower scores mean less neuropathy):* 2 mg: 2.81 4 mg: 3.27 PL: 2.56; $P =$ NS *VPT great toe (lower scores mean less neuropathy):* 2 mg: 6.65, 4 mg: 8.18, PL: 6.09; $P =$ NS	NR

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
	Koeppen 2004[52]	Vinca alkaloid	150 total; Org: 75, PL: 75	2 mg given as subcutaneous injection 1-3 h before and after administration of VCR. Four weeks after discontinuation of VCR treatment (plus or minus 1 wk) the final two injections were given at least 2-h apart	NR	NR	NR	*Neuropathy-free interval**: no significant difference between the two groups ($P > .14$)
	Van Gerven 1994[56]	Cisplatin	55 randomized, 42 evaluable; Org: 19, PL: 23	2 mg/d subcutaneously injected for 5 consecutive days	NR	NR	*Vibratory threshold slopes* (changes from baseline as opposed to a comparison to each other):* Org: $P = .06$ PL: $P < .001$ *Abnormal VPT at 3-5 mo:* Org: 50%, PL: 75%, RR‖ = 0.67 (95% CI, 0.31 to 1.43); $P = .30$	NR
	van Kooten 1992§[27]	Vinca alkaloids	28 total; Org: 13, PL: 15	Subcutaneous injections of 2 mg Org 2766 to patients with non-Hodgkin lymphoma on days 1 and 10 of each chemotherapy course and to patients with Hodgkin disease on days 1 and 8 of each chemotherapy course	NR	NR	*Total number of patients receiving sensory disturbances (impaired touch and pain perception in hands and/or feet and/or abnormal position sense in the hallux muscle)* Org: 2, PL: 60; $P < .05$	*Total number of sensory complaints reported including pain, paresthesias, and numbness during three follow-up visits:* Org: 28, PL: 61; $P = NS$ *Total number of complains of numbness alone:* Org: 9 PL: 29 $P < .05$

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
	Hovestadt 1992§¶[55]	Cisplatin	18 total; Org low: 5, Org high: 6, PL: 7	Low (0.25 mg/m^2) or high (1 mg/m^2) dose subcutaneously injected before the start of cisplating and 24 h later	NR	NR	*Mean VPT at 1 mo:* Org low: 2.9, Org high: 1.1, PL: 3.7 *Mean VPT at 4-12 mo:* Org low: 3.6, Org high: 2.0, PL: 4.8 *Note: No formal test for significance conducted*	*Mean sum scores for patient reported neurological signs and symptoms at 1 mo:* Org low: 6.3, Org high: 0.0, PL: 6.3 *Mean sum scores for patient reported neurological signs and symptoms at 4-12 mo:* Org low: 4.5, Org high: 3.5, PL: 5.7 *Note: No formal test for significance conducted*
Oxycarbazepine (OXC)	Argyriou2006a[35]	Oxaliplatin	40 total; OXC: 20, unblinded control group: 20	150 mg/d initially then doubled on a weekly basis up to maximum target dose of 600 mg two times a day (1200 mg/d)	*Incidence assessed by NSS:* OXC: 31.2%, unblinded control group: 75%; $P = .033$ (EFF population) $P = .050$ (ITT population) RR = 0.42 (95% CI, 0.19 to 0.91)	*Severity as measured by mean TNS:* OXC: 4.1 ± 6.5 (range 0-17), unblinded control group: 11.2 ± 9.1 (range 0-28); $P = .016$	*Between-group comparisons (V1 v V4 values) of the mean a-SAP* changes: S.Per/al a-SAP: $P = .03$ Sural a-SAP: $P = .047$ The following were statistically non-significant: Ulnar a-SAP; Ulnar a-CMAP; Ulnar MCV; Per/al a-CMAP; Per/al MCV	*Mean neuropathy disability score:* OXC: 5.1 ± 8.2, unblinded control group: 20.0 ± 23.1; $P = .021$ *Mean Neuropathy Symptom Score:* OXC: 0.6 ± 0.9, unblinded control group: 1.5 ± 1.3; $P = .025$
Retinoic acid (RA)	Arrieta2011§[59]	Cisplatin + paclitaxel	92 total; RA: 45, PL: 47	20 md/m^2/d	*Neuropathy grade ≥ 2, assessed by NCI criteria:* RA: 56% (95% CI, 39% to 67%), PL: 75% (95% CI, 64% to 86%); $P = .056$	NR	*Differences in amplitude damage at baseline and post-treatment:* RA: 28.3s, PL: 38.4s; $P = .05$	NR
rhuLIF	Davis 2005[21]	Paclitaxel + Carboplatin	117 total; rhuLIF low: 36, rhuLIF high: 39, PL: 42	rhuLIF at two doses of either 2 μg/kg/d or 4 μg/kg/d	NR	*Change in CPNE score from BL to after 4 cycles**: No significant difference between groups	*Change in the velocity of median nerve from BL to after 4 cycles*†: rhuLIF: 1.2 m/s worse conduction, PL: 2.7 m/s better conduction; P = NS	*QLQ-30 and CIPNS-32*†‡: rhuLIF patients reported significantly greater improvements in global health status and significant reductions in level of fatigue compared with placebo patients

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
Venlafaxine	Durand 2012[29]	Oxaliplatin	48 total Ven: 24 PL: 24	50 mg 1 h prior oxaliplatin and venlafaxine extended release 37.5 mg two times a day from day 2 to 11	NR	*NPSI - pins and needles†:* venlafaxine: −1.39, PL: −0.26; $P < .001$ *NPSI - pain triggered by cold†:* venlafaxine: −0.59, PL: −0.05; $P = .06$	NR	*Full relief of acute NeurotoxicityP:* venlafaxine: 31.3% PL: 5.3% $P = .03$ *Functional impairment in ADL†:* venlafaxine: −0.67, PL: +0.69; $P < .001$
Vitamin E	Kottschade 2011[45]	Taxane or platinum	207 total; Vit E:103, PL: 104	300 mg two times per day for 1 mo beyond completion of chemotherapy	*Grade 2+ sensory neuropathy assessed by NCI-CTC classification*:* Vit E: 34% (95% CI, 25.0% to 44.8%), PL: 29% (95% CI, 20.1% to 39.4%) ; $P = .43$ *Median time to onset†:* Vit E: 58 d (95% CI, 43 to 97 d), PL: 69 d (95% CI, 49 to 105 d); $P = .58$	*Median time to resolution to ≤ grade 1 sensory neuropathy†:* Vit E: 36 d (95% CI, 28 to 44 d), PL: could not be established because only 6 of 27 patients had resolution of ≥ grade 2 sensory neuropathy	NR	NR
	Argyriou, 2006[22]	Paclitaxel	30 total; Vit E: 14, unblinded control group: 16	300 mg two times per day during chemotherapy and up to 3 mo after	*Incidence assessed by NSS*:* Vit E: 21.4%, unblinded control group: 68.5%; $P = .026$ (EFF population) Vit E: 31.3%, unblinded control group: 68.4%; $P = .030$ (ITT population) RR = 2.51 (95% CI, 1.16 to 5.47)	*Mean PNP score†:* Vit E: 4.99 ± 1.33, unblinded control group: 10.47 ± 10.62; $P = .023$	*Changes in mean electrophysiological scores from BL to subsequent scores between groups†:* Ulnar a-SAP: $P = .021$; S. Per/al a-SAP: $P = .017$; Sural a-SAP: $P = .046$ The following were statistically nonsignificant: Ulnar a-CMAP, Ulnar MCV, Per/al a-CMAP, Per/al MCV	NR
	Pace 2003§[33]	Cisplatin	47 total but only 27 reported; Vit E: 13, unblinded control group: 14	300 mg/d before chemotherapy and sustained for 3 mo after the cessation of cisplatin treatment	Vit E: 30.7%, unblinded control group: 85.7%; $P < .01$ RR = 0.36 (95% CI, 0.15 to 0.83) $P < .001$	*Severity as measured by neurotoxicity score:* Vit E: 2.1 ± 2.1, unblinded control group: 4.7 ± 2.9; $P < .01$	*Mean Sural SCV change from baseline:* Vit E: −1.6, unblinded control group: −3.5; $P < .01$ *Median amplitude change from baseline:* Vit E: −3.1, unblinded control group: −6.3; $P < .01$	NR

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Table 2. Randomized Controlled Trials Regarding the Prevention of CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief, and/or Other Patient-Reported Outcomes
	Pace 2010§[46]	Cisplatin	108 total; Vit E: 54, PL: 54	400 mg/d before chemotherapy and sustained for 3 mo after the cessation of cisplatin treatment	*Neurotoxicity incidence higher than grade 3 of* TNS*:* Vit E: 5.9%, PL: 41.7%; $P < .01$; RR = 0.14 (95% CI, 0.02 to 1.00), $P < .05$	*Severity as measured by neurotoxicity score (TNS):* Vit E: 1.4 ± 1.5, PL: 4.1 ± 4.5; $P < .01$	*Mean Sural amplitude change from baseline:* Vit E: −3.9, PL: −5.5 *Median amplitude change from baseline:* Vit E: +0.1, PL: −2.8	NR

Abbreviations: ADL, activities of daily living; AUC, area under the curve; CIPNS, chemotherapy-induced peripheral neuropathy survey; DEB-NTS, Debiopharm Neurotoxicity Scale; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire FACT/GOG-Ntx, Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group- Neurotoxicity scale; FACT-TOI, Functional Assessment of Cancer Therapy Scale - Taxane Trial Outcome Index; GOG, Gynecologic Oncology Group; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; NA, not applicable; NCS, nerve conduction studies; NDS, Neurological Disability Score; NR, not reported; NS, not significant; NSS, Neurological Symptom Score; OSS, oxaliplatin-specific scale; PL, placebo; PN, peripheral neuropathy; PNP, peripheral neuropathy score; QLQ-C30, European Organization for the Treatment of Cancer quality of life questionnaire-30 items; QOL, quality of life; RR, risk ratio; rTNT, reduced Total Neuropathy score; SCV, sensory conduction velocity; SNAP, sensory nerve action potentials; SWOG, South West Oncology Group; TNS, Total Neuropathy Score; VPT, vibration perception threshold.

*Primary end point of study.

†Secondary end point of study.

‡Higher scores reflect less neurotoxicity, better functional status, and less fatigue, respectively.

§Primary or secondary end points not reported.

‖Risk ratio calculated and reported in Albers et al (2011).

¶This is a follow-up study to Van der Hoop 1990, reporting on a subset of longer-term follow-up patients.

can be argued that the effectiveness of GSH for decreasing platinum-associated neurotoxicity should be further evaluated in a large, methodologically rigorous trial.

The efficacy of the ACTH[4-9] analog Org 2766 for the prevention of cisplatin- and vincristine-based neuropathy was assessed in six placebo-controlled trials.[27,52-56] Patients in these trials were randomly allocated to subcutaneous injections of Org 2766 at doses that ranged from 0.25 to 4.0 mg/kg. The first of these trials,[53] involving 55 patients in a three-arm study (low dose, higher dose, and placebo), reported a substantial reduction in neuropathy associated with this agent. A subsequent report,[55] involving 18 of the same patients with longer follow-up, reported additional benefit from Org 2766. Another report[56] which involved multiple authors in common with the previous two reports, again with a relatively small number of patients (42 evaluable patients among two arms), also supported that this agent was helpful for decreasing cisplatin-associated neuropathy. A subsequent Dutch trial, involving 28 patients receiving vincristine, also reported positive results. In contrast to these multiple small trials, two larger well-conducted trials[52,54] were unable to provide any suggestion that this agent decreased CIPN; in fact, the neuropathy was numerically worse with the study agent in one of the trials.[54]

Hershman et al compared acetyl-L-carnitine (ALC) at a dose of 3,000 mg per day with placebo in 409 women with breast cancer undergoing adjuvant taxane-based chemotherapy. Unexpectedly and alarmingly, a statistically significant increase in CIPN was reported in patients receiving ALC ($P = .01$) at 24 weeks, although no difference was observed at 12 weeks, the primary outcome of the trial. This is the first trial to support that a nutritional supplement increased CIPN.[57]

Five remaining trials considered the prophylactic effect of nutritional supplements on CIPN. One pilot trial,[24] investigating long-term supplementation with glutamate for the prevention of CIPN in 43 women with ovarian cancer, failed to show a benefit in patients receiving the supplement compared with placebo controls. Another pilot study[28] investigating the efficacy of glutamine found that oral glutamine significantly reduced the incidence and severity of CIPN in 86 patients receiving oxaliplatin. However, this study was neither blinded nor placebo controlled, thus these findings should be interpreted with caution. A trial of 57 patients with breast cancer examined the efficacy of omega-3 fatty acids for the prevention of paclitaxel-induced neurotoxicity,[58] reporting a significant difference in CIPN incidence favoring patients in the omega-3 fatty acids arm over those in the placebo arm (odds ratio = 0.3; 95% CI, 0.10 to 0.88, $P = .029$). This promising-appearing result has not been replicated. A placebo-controlled trial[59] evaluating all-*trans* retinoic acid (20 mg/m^2/d) in 95 patients with non–small-cell lung cancer found a trend toward a lower rate of ≥ grade 2 neuropathy ($P = .056$) and axonal degeneration, as demonstrated by nerve conduction velocity ($P = .05$) in the all-*trans* retinoic acid group. In 2011, Nishioka et al[34] reported on the efficacy of the Kampo medicine, goshajinkigan (GJG), for peripheral neuropathy associated with oxaliplatin therapy. Among 45 patients with colorectal cancer randomized to oral GJG or an unblinded control arm, the incidence of grade 3 peripheral neuropathy in the GJG group was significantly lower than in the control group ($P < .01$). No other reports regarding GJG are available. In the final trial, Gandara et al[60] failed to demonstrate a significant chemoprotective effect against cisplatin-induced toxicities with diethyldithiocarbamate (DDTC) in 221 patients; in addition this therapy was associated with increased treatment toxicities and lower levels of cisplatin administration.

Clinical Interpretation

To date, trials of agents used in cancer patients for the prevention of CIPN have not shown any consistent and/or conclusive clinically meaningful benefits when compared with placebo controls. The strength of the evidence for venlafaxine was inadequate and thus not strong enough to recommend it for use in routine clinical practice (Table 3). This result is consistent with the systematic Cochrane review on the treatment of platinum drug–induced peripheral neurotoxicity.[61] Additional work evaluating venlafaxine would be welcomed.

TREATMENT

Trial Results

Six trials investigated antidepressants, anticonvulsants, and a topical gel for the treatment of CIPN[62-67] (Table 4).

Smith et al[62] studied the effect of duloxetine in a randomized, placebo-controlled, cross-over trial of 231 patients with CIPN. Patients received 30 mg of duloxetine or placebo for the first week and 60 mg of duloxetine or placebo for 4 more weeks. Patients who received duloxetine reported a significant decrease in average pain compared with those who received placebo ($P = .003$). In addition to a decrease in pain, data from the trial also supported that duloxetine decreased numbness and tingling symptoms. Results from an exploratory subgroup analysis suggest that duloxetine may be more efficacious for oxaliplatin-induced, as opposed to paclitaxel-induced, painful neuropathy.

Two small trials[65,66] investigated the efficacy of the tricyclic antidepressants amitriptyline (target maximum dose of 50 mg/d) and nortriptyline (target maximum dose of 100 mg/d) in treatment of CIPN. These trials failed to demonstrate any significant improvements in patient-reported sensory symptoms or QOL, as measured by the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30[66] and a horizontal visual analog scale.[65] One trial[66] terminated patient recruitment early as a result of poor recruitment rates. Similarly, two trials[63,64] evaluating the effects of anticonvulsants on CIPN were unable to demonstrate any benefit for either gabapentin at a target dose of 2,700 mg/d[64] or lamotrigine at a target dose of 300 mg/d.[63] Primary outcome measures in both studies included average pain as measured by a numerical rating scale and the Eastern Cooperative Oncology Group neuropathy scale.

Finally, one trial NCCTG N06CA,[67] evaluated a compounded topical gel treatment manufactured by Gateway Compounding Pharmacy in Bismark, ND, each 1.31 g measured dose containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg). In 208 randomly allocated patients, a trend was reported toward improvements in the EORTC Quality of Life Questionnaire–Chemotherapy-Induced Neuropathy 20 sensory subscale scores ($P = .053$), whereas a significant improvement was reported in motor subscale scores ($P = .021$).

Clinical Interpretation

Duloxetine is recommended for clinical practice in patients with painful CIPN, based on efficacy data from a large randomized placebo-controlled trial,[62] the results of which are consistent with the established efficacy of duloxetine in patients with painful diabetic

Table 3. Summary of Recommendations

Interventions	Strength of Recommendation	Strength of Evidence	Benefits	Harms*	Additional Comments
Prevention					
Acetylcysteine	Inconclusive	Low	Low	Low	One very small randomized trial looked promising.
Acetyl-L -carnitine	Strong against	High	No evidence of efficacy	High	A phase III trial (N = 409) found no evidence of efficacy and an unexpected increase in CIPN at 24 wk in active arm.
Amifostine	Moderate against	Intermediate	Low	Moderate	While several trials supported that neuropathy might be a little better with the active treatment arm, there was substantial associated toxicity.
Amitriptyline	Moderate against	Intermediate	No evidence of efficacy	Moderate	Negative, reasonably-sized phase III trial with significant difference in toxicities.
Calcium and magnesium	Moderate against	High	Low	Low	Negative large phase III trial (and 3 smaller placebo-controlled trials) did not substantiate uncontrolled data reports and a positive trial that was prematurely closed.
Carbamazepine/ oxycarbazepine	Inconclusive	Low	Low	Low	Two relatively small trials, one of which was neutral and one of which suggested benefit, although with an unblinded control arm.
Diethyldithio-carbamate	Strong against	Low	No evidence of efficacy	High	Active treatment arm had more toxicity, more patients likely to stop chemotherapy as a result of toxicity, and lower cisplatin cumulative doses.
Glutamate/glutamine	Inconclusive	Low	Low	Low	Two small- to moderate-sized trials, which suggested some benefit in some measures of neuropathy.
Glutathione for paclitaxel/carboplatin	Moderate against	Intermediate	Low	Low	One reasonably-sized trial which was convincingly negative.
Glutathione for cisplatin or oxaliplatin	Inconclusive	Low	Low	Low	Six small trials, five of which suggested benefit along with the trial that looked at *N*-acetyl-cysteine (which increases serum glutathione concentrations), detailed earlier in this table.
Goshajinkigan (Kampo medicine)	Inconclusive	Low	Low	Low	Forty-five patient trial, with unblinded control arm, that suggested benefit.
Nimodipine	Strong against	Low	No evidence of efficacy	Moderate	Worse outcome for active arm.
Omega 3	Inconclusive	Low	Low	Low	57 patient trial that supported benefit for the active treatment arm.
Org 2766	Moderate against	Intermediate	Low	Low	Four reports regarding 3 small trials which suggested benefit but negative results from 2 larger well conducted trials, one of which reported worse outcome for active arm (Roberts 1997).
Retinoic acid	Moderate against	Low	Low	Moderate	One small RCT with unblinded control group and significant difference in toxicities.
rhuLIF	Moderate against	Low	No evidence of efficacy	Low	Worse neuropathy endpoints in the active therapy arm for changes in velocity in the median nerve.
Venlafaxine	Insufficient	Intermediate	Moderate	Moderate	A small randomized trial that was a mixture between a prevention versus a treatment trial was associated with many positive *P* values suggesting benefit.
Vitamin E	Moderate against	Intermediate	Low	Low	While three small randomized trials were reported as showing benefit, a larger phase III trial was convincingly negative.
Treatment					
Acetyl-L -carnitine	Inconclusive	Low	Low	Moderate	While a positive phase III trial was reported in abstract form only, note that a prevention trial was associated with more neuropathy related to this agent.
Duloxetine	Moderate for	Intermediate	Moderate	Low	Phase III trial positive, overall, for treatment of oxaliplatin or paclitaxel neuropathy. Subset analysis suggested that benefit may be primarily with oxaliplatin-induced neuropathic pain.
Gabapentin	Inconclusive	Intermediate	Low	Low	Single negative phase III trial, but data supportive of benefit in other forms of neuropathy and clinical experience in CIPN support further study and clinical consideration.
Lamotrigine	Moderate against	Intermediate	No evidence of efficacy	Low	Negative phase III trial and data in non-CIPN neuropathy are not impressive.
Nortriptyline/amitriptyline	Inconclusive	Intermediate	Low	Low	Two small low-power phase III trials with numerical data favoring the active treatment arms.
Topical amitriptyline, ketamine, ± Baclofen	Inconclusive	Intermediate	Moderate	Low	Phase III trial of compounded topical preparation from Gateway Compounding Pharmacy in Bismark, ND, that delivered 1.31-gm dose containing amitriptyline HCl 40 mg, Baclofen 10 mg and ketamine 20 mg in a pluronic lecithin organogel, with data suggesting that the active arm decreased sensory neuropathy ($P = .053$) and motor neuropathy ($P = .021$).

Abbreviations: CIPN, chemotherapy-induced neuropathy; RCT, randomized controlled trial.
*"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.

Table 4. Randomized Controlled Trials on the Treatment of Established CIPN

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief and/or Other Patient-Reported Outcomes
Duloxetine (Dulox)	Smith, 2013[62]	Taxane or platinum	231 total; Grp A: 115, drug then cross over to placebo; Grp B: 116, placebo then cross over to drug	30 mg for 1 week and then 60 mg daily for 4 additional weeks	NA	*Relative risk benefit of 30% pain reduction with duloxetine*^{SA}*:* RR: 1.96 (95% CI,1.15 to 3.35) *Relative risk benefit of 50% pain reduction with duloxetine*^{SA}*:* RR: 2.43 (95% CI,1.11 to 5.30)	NR	*Average pain (mean change score) as measured by BPI-SF*:* Dulox first: 1.06 (95% CI, 0.72-1.40), PL first: 0.34 (95% CI, 0.01 to 0.66); $P = .003$; effect size = 0.513 *Mean change in FACT/GOG-Ntx total score)*^{S}*:* Dulox first: 2.44 (95% CI, 0.43 to 4.45), PL first: 0.87 (95% CI, −1.09 to 2.82); $P = .03$ *Mean difference in mean change score:* 1.58 (95% CI, 0.15 to 3.00)
Gabapentin (G)	Rao, 2007[64]	Vinca alcaloids, platinum, or taxanes	115 total; G/P arm: 57, P/G arm: 58	Gabapentin increased to target dose of 2,700 mg daily, for 6 wk, then 2 wk washout, followed by 6 wk of placebo	NA	NR	NR	*Changes in patient-reported multiple baseline pain and neuropathy scores similar in both treatment arms** *Similar changes in analgesic use, quality of life, and global impression of change scores between study arms*^{S}*.*
Lamotrigine (LAM)	Rao, 2008[63]	Vinca alcaloids, platinum, or taxanes	131 total; LAM: 63, PL: 62	Lamotrigine 25 mg for 2 wk, 25 mg twice daily for 2 wk, 50 mg twice daily for 2 wk, 100 mg twice daily 2 wk, 150 mg twice daily 2 wk	NA	*Mean decrease in symptom severity (measured by ENS)*:* LAM: 0.4, PL: 0.3; $P = .36$	NR	*Mean decrease in average pain score (measured by ENS)*:* LAM: 0.3, PL: 0.5; $P = .56$ *Subject Global Impression of Change:*^{S} *LAM: 17.6%, PL: 17.4%; $P = .4$*
Nortriptyline (No.)/ amitriptyline (AMI)	Hammack, 2002[65]	Cisplatin	51 total; N/PL: 26, PL/N: 25	Nortriptyline 25 mg daily, increasing weekly to maximum target dose 100 mg daily in a 4-wk phase followed by a second placebo phase (order reversed for arm B)	NA	NR	NR	*No significant differences in paresthesia* were observed in the first treatment period between nortriptyline and placebo ($P = .78$)* *Clinically significant decrease in pain as measured by VAS*^{S}*:* first treatment period; N: 30%, P: 33%; $P = .99$ *Mean QOL scores as measured by VAS*^{S}*:* first treatment period: N: −4.6, P: −7.7; $P = .74$
	Kautio, 2008[66]	Vinca alcaloids, platinum or taxanes	44 total	10 mg/d up to max of 50 mg/d, followed by a stable dose ≥ 4 wk	NA	*Severity of neuropathy assessed by NCI criteria*^{S}*:* no significant differences between groups	NR	*Mean global improvement assessed by diary data*:* AMI: 3.4 ± 3.6, PL: 1.9 ± 3.1; P = NS *Global improvement assessed by VRS at final visit*:* AMI: −47%, PL: −31%; P = NS *EORTC-C30*^{S}*:* amitriptyline significantly improved QOL over placebo ($P = .038$) *Depression and Sleep*^{s}*:* no significant changes in the depression scale in either group and no differences between groups *Physical Activity*^{S}*:* no significant difference between groups

(continued on following page)

Table 4. Randomized Controlled Trials on the Treatment of Established CIPN (continued)

Pharmacologic Agent	Authors and Study Design	Neurotoxic Chemotherapy Agent	Patients (No.)	Intervention Dose	Incidence of Neuropathy	Severity of Neuropathy	Neurophysiologic or Instrumental Investigations	QOL, Symptom Relief and/or Other Patient-Reported Outcomes
Topical amitriptyline, ketamine, ± Baclofen (BAK)	Barton, 2011[67]	Vinca alkaloids, platinum, taxanes or thalidomide	208 total	Compounded gel containing baclofen10 mg, amitriptyline HCL 40 mg, and ketamine 20 mg, application to affected area twice daily for 4 wk	NA	*EORTC CIPN-20 mean neuropathy change from BL to 4 wk*[*]: *Sensory subscale:* BAK: 8.1 ± 15.05, PL: 3.8 ± 15.52; difference: 4.3; (95% CI, −0.6 to 9.3); $P = .053$ *Motor subscale:* BAK: 7.1 ± 13.72, PL: 1.8 ± 14.05; difference: 5.3; (95% CI, 0.9 to 9.7); $P = .021$ *Autonomic subscale:* BAK: 3.3, PL: 1.7; difference: 1.6; (95% CI, −4.0 to 7.1); $P = .580$	NR	*Brief Pain Inventory*[S]: no significant difference between groups *Profile of Mood States*[S]: no significant difference between groups

Abbreviations: ADL, activities of daily living; AUC, area under the curve; CIPNS, chemotherapy-induced peripheral neuropathy survey; DEB-NTS, Debiopharm Neurotoxicity Scale; ECOG, Eastern Cooperative Oncology Group; ENS, Eastern Cooperative Oncology Group neuropathy scale; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group-Neurotoxicity scale; FACT-TOI, Functional Assessment of Cancer Therapy Scale-Taxane Trial Outcome Index; GOG, Gynecologic Oncology Group; NA, not applicable; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NCS, nerve conduction studies; NDS, Neurological Disability Score; No. of patients, No. of patients randomly assigned; NR, not reported; NS, not significant; NSS, Neurological Symptom Score; OSS, oxaliplatin-specific scale; PL, placebo; PN, peripheral neuropathy; PNP, peripheral neuropathy score; QLQ-C30, European Organisation for the Treatment of Cancer quality of life questionnaire-30 items; rTNT, reduced Total Neuropathy Score; SCV, sensory conduction velocity; SNAP, sensory nerve action potentials; SWOG, South West Oncology Group; TNS, Total Neuropathy Score; VPT, vibration perception threshold.

[P]Primary end point of study.

[S]Secondary end point of study.

[SA]Subgroup analysis.

[*]Primary or secondary end points not reported.

peripheral neuropathy. It is important to note that this trial predominantly included patients with breast and gastrointestinal malignancies with grade 1 or higher sensory neuropathy and a score of at least 4 on a scale of 0 to 10 representing average chemotherapy-induced pain 3 or more months after treatment completion. Like all clinical trials, data showing a benefit for patients that do not match the study criteria are not known. Exploratory subgroup analysis suggests that duloxetine may work better for oxaliplatin-induced, as opposed to paclitaxel-induced, painful neuropathy. Ideally, all findings from this trial should be confirmed. In the meantime, clinicians should be prepared to weigh the recommendations for their individual patients with the potential risks and adverse effects. Lamotrigine is not recommended for clinical practice because of limited evidence of efficacy for CIPN or other forms of neuropathy (and because there is a risk of Stephens-Johnson syndrome associated with lamotrigine).

While none of the other studied compounds meet the criteria to be formally recommended for clinical practice at this time, there are three options that may be offered for patients despite not yet having been proven to be helpful for CIPN. These options are (1) a tricyclic antidepressant (such as nortriptyline); (2) gabapentin or another medication with the same mechanism of action, pregabalin; and (3) a compounded topical gel containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg). The reasons to consider these options are (1) the magnitude of the unmet need for treating established CIPN, (2) methodological concerns about the quality of the trials, and (3) the relative safety of these agents. However, there are limitations to using these agents. First, the tricyclic agents can cause toxicity, especially in elderly patients. Second, there is a single negative randomized trial evaluating gabapentin for the treatment of CIPN (which may have been underpowered and did not have painful CIPN as the primary end point). Third, although a trial of topical baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg) decreased CIPN symptoms, this compounded agent is not commercially available and can only be manufactured by a compounding pharmacy. In addition, the long-term safety of this preparation has not been established.

DISCUSSION

Unfortunately, these guidelines do not make any recommendations for clinical practice regarding agents to prevent CIPN, other than decreasing the dose or duration of an offending cytotoxic agent. With regard to recommendations about the treatment of established CIPN, these guidelines do make some treatment recommendations and considerations (Table 3). This raises a reasonable question: why were these guidelines developed?

The decision to develop these guidelines was based on the magnitude of the clinical problem and the moderate body of work that has been completed to understand potential means of preventing and/or treating this prominent condition. These guidelines were designed to portray the problem, provide a current and comprehensive evidentiary base, and develop clinical recommendations for or against the use of studied therapies.

In addition to the single positive recommendation for duloxetine for the treatment of established CIPN pain, the conclusions of this committee include recommendations about what should not be routinely used in practice, despite some initial promising studies suggesting usefulness. A moderate recommendation is made against the use of lamotrigine for the treatment of established CIPN, and moderate to strong recommendations are made against the following agents for the prevention of CIPN: ALC , amifostine, amitriptyline, intravenous CaMg, DDTC, nimodipine, Org 2766, retinoic acid, rhuLIF, and vitamin E.

The current work sets the stage for future guideline updates as new evidence arises. As such, it is worthwhile to discuss thoughts about future CIPN research. First, studies regarding the basic mechanisms of CIPN are encouraged. The same is true regarding studies related to the clinical manifestations and measurement of this problem. The identification of valid and reproducible tools to assess the extent and severity of CIPN is needed to define the best end points for clinical trials.[3,4] Moreover, the recognition of differences between patient-reported, clinician-reported, and objective outcomes should be carefully considered.[1,68-71] To this end, it is reasonable to summarize current thoughts about how to measure CIPN, which is primarily a sensory problem, in clinical trials. First, it is well accepted that PRO measures of sensory CIPN are preferred over clinician-determined assessments. Second, there are several PRO CIPN measures, which have strong psychometric properties, that have been extensively studied, including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 scale, the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity tool, and the Total Neuropathy Score (a mixture of PRO and physical examination measures).[3,72-81] Lastly, recent work comparing such tools does note that they each have strengths and that no clear-cut winner can be declared.[4,71]

The identification of new agents to prevent and/or treat CIPN is essential. An example of an agent that appears promising for the potential prevention of CIPN is minocycline, primarily based on encouraging preclinical data.[82-84] Also, the preliminary data supporting that GSH may be helpful for platinum-caused neuropathy, reviewed above, deserves further evaluation, despite a negative trial that was unable to support the utility of GSH for the prevention of paclitaxel-induced neuropathy. In addition, evidence supporting the potential efficacy of venlafaxine for prevention of oxaliplatin-induced CIPN provides a compelling impetus for further study of venlafaxine and/or duloxetine for preventing CIPN.

More studies are also warranted to better define how individual patient genetic variations may contribute to differences in the development of CIPN.[85] To this end, a research group sequenced 20,794 genes associated with heredity neuropathy from patients who had received paclitaxel-based chemotherapy and reported that *EPHA5*, *ARHGEF10*, and *PRX* are associated with the likelihood of developing CIPN.[86] Novel genetic markers of paclitaxel-induced sensory peripheral neuropathy have also been preliminarily identified and include a common polymorphism in the congenital peripheral neuropathy gene, *FGD4*[87] and the *CYP2C8* gene, which is responsible for metabolizing paclitaxel,[88] and the Fanconi anemia complementation group of genes (*FANCD2*).[89] Future identification of patients at an increased risk of peripheral neuropathy may inform the use of alternative therapy and/or the clinical management of this toxicity.[87]

With regard to potential study ideas for the treatment of established CIPN, it could be argued that further study is needed to evaluate the efficacy and safety of a number of topical therapies. Additional

data regarding a topical gel treatment containing baclofen, amitriptyline HCL, and ketamine for patients who have symptomatic CIPN would be helpful. Another promising agent is topical menthol. Menthol is a topical cooling compound that selectively activates TRPM8 receptors, which are upregulated after sensory nerve injury. A phase II clinical trial of topical 1% menthol in 29 patients with painful CIPN showed that 83% demonstrated pain improvement after 4 to 6 weeks.[90] A second open-label study of 1% topical menthol twice daily in 27 patients with CIPN reported that 75% of the subjects had a 10% decrease and 50% showed over 30% decrease in self-reported symptoms.[91] This supports the further investigation of menthol for treating established CIPN. Topical capsaicin preparations have also been used to effectively treat peripheral neuropathic pain. However, evidence of its effectiveness in CIPN has not yet been established. Trials investigating the efficacy of high-dose capsaicin preparations for severe CIPN are of interest.

Given the prominent clinical use of gabapentin and pregabalin in clinical practice, the demonstrated efficacy of these drugs for treating other types of neuropathy pain, and that only one phase III trial has been done in patients with established CIPN, another phase III trial of either drug would also be of great value.

EXTERNAL REVIEW

A draft of the clinical practice guideline was reviewed by two Clinical Practice Guideline Committee members and 12 Survivorship Guideline Advisory Group members. In addition to providing comment and feedback, practitioners were asked to judge the evidence review and agreement with the recommendations. One additional reviewer was asked to assess the clarity of the recommendations and ease of implementation. The evidence review was rated as high quality, and there was high agreement with the substance of the recommendations.

The compounded topical baclofen-amitriptyline-ketamine gel was identified as having barriers to implementation. The product was created by one compounding pharmacy for a trial, and the combination is not US Food and Drug Administration approved. Lack of insurance reimbursement for compounded products was also raised. Although not a recommended treatment, the statement regarding the topical gel as an option comes with a qualifier that specifies patients should be informed about the limited scientific evidence, potential harms, benefits, and costs.

RECOMMENDATIONS

The following recommendations are evidence based, informed by generally small RCTs, and guided by clinical experience. Ratings for benefits, harms, evidence quality, and recommendation strength are provided in Table 3 (see Appendix Table A1 for rating definitions).

PREVENTION OF CIPN

There are no established agents recommended for the prevention of CIPN in patients with cancer undergoing treatment with neurotoxic agents. This is based on the paucity of high-quality, consistent evidence and a balance of benefits versus harms.

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

- ALC
- amifostine
- amitriptyline
- CaMg for patients receiving oxaliplatin-based chemotherapy
- DDTC
- GSH for patients receiving paclitaxel/carboplatin chemotherapy
- nimodipine
- Org 2766
- all-*trans* retinoic acid
- rhuLIF
- vitamin E.

Venlafaxine is not recommended for routine use in clinical practice. Although the venlafaxine data resulted in some support for its utility, the data were not strong enough to recommend its use in clinical practice until additional supporting data become available.

No recommendations can be made on the use of *N*-acetylcysteine, carbamazepine, glutamate, GSH (for patients receiving cisplatin or oxaliplatin-based chemotherapy), GJG, omega-3 fatty acids, or oxycarbazepine for the prevention of CIPN at this time.

TREATMENT OF CIPN

For patients with cancer experiencing CIPN, clinicians may offer duloxetine

No recommendations can be made on the use of.

- ALC, noting that a positive phase III abstract supported its value, but this work has not yet been published in a peer-reviewed journal, and a prevention trial suggested that this agent was associated with worse outcomes.
- Tricyclic antidepressants; however, based on the limited options that are available for this prominent clinical problem and the demonstrated efficacy of these drugs for other neuropathic pain conditions, it is reasonable to try a tricyclic antidepressant (eg, nortriptyline or desipramine) in patients suffering from CIPN after a discussion with the patients about the limited scientific evidence for CIPN, potential harms, benefits, cost, and patient preferences.
- Gabapentin, noting that the available data were limited regarding its efficacy for treating CIPN. However, the panel felt that this agent is reasonable to try for selected patients with CIPN pain given (1) that only a single negative randomized trial for this agent was completed, (2) the established efficacy of gabapentin and pregabalin for other forms of neuropathic pain, and (3) the limited CIPN treatment options. Patients should be informed about the limited scientific evidence for CIPN, potential harms, benefits, and costs.
- A topical gel treatment containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg), noting that a single trial supported that this product did decrease CIPN symptoms. Given the available data, the panel felt that this agent is reasonable to try for selected patients with CIPN pain. Patients should be informed about the limited scientific evidence for the treatment of CIPN, potential harms, benefits, and costs.

SPECIAL COMMENTARY

A number of nonpharmacologic interventions have been investigated for their role in preventing or treating peripheral neuropathy. However, the paucity of RCT evidence prohibited inclusion of those studies in this systematic review. Moreover, the studies were often conducted in diabetic populations, with no specific focus on CIPN. Nevertheless, several of the interventions have been tested in populations that included patients with cancer experiencing CIPN and, as such, merit further examination.

Evidence of the efficacy and effectiveness of one such intervention, acupuncture, was systematically reviewed by Franconi et al for the treatment of CIPN.[92] Seven clinical studies of varying designs and methodological rigor were identified. Although there were some indications of improvement in symptoms and pain scores in most included studies, the current available evidence is limited. Evidence of efficacy of electrocutaneous nerve stimulation in relieving refractory chronic pain[93] led investigators to test its potential in patients with CIPN. A small pilot study specifically tested the MC5-A Calmare device on 16 patients with refractory CIPN.[94] The device, which is hypothesized to provide "nonpain" information to the cutaneous nerves to block the effect of pain, showed an improvement in pain scores (59% reduction at 10 days, $P < .001$) with no reported adverse effects. However, a placebo-controlled, randomized, small (14 total patients) trial, published only as an abstract, was unable to demonstrate a benefit for scrambler therapy.[95] Randomized controlled evaluation of the efficacy of electrocutaneous nerve stimulation in CIPN is ongoing. The use of other complementary or alternative medicine modalities in patients with CIPN is expanding.[96]

PATIENT AND CLINICIAN COMMUNICATION

CIPN is a serious adverse effect of certain therapies that can interfere with the efficacy of treatment and decrease quality of life. It is important for the physician to initiate discussion of the potential for CIPN as the patient, who can be overwhelmed by the cancer diagnosis and treatment regimen, may not want to burden the clinician with additional concerns and they may think that early CIPN symptoms are imaginary. Indeed, the patient may not recognize the potential for more permanent damage. Therefore, it is important that the clinician address the potential intensity and symptomatic variants of CIPN. Also, because there is opportunity to decrease the CIPN if it is reported and recognized early, the clinician needs to be alert to its genesis. This might be accomplished by an initial discussion with the patient of the potential for CIPN followed by regular symptomatic assessments. If a numeric scale is used, it is important to augment the scale number with discussion of the actual symptoms and their impact on quality of life. While there may be instances where CIPN must be tolerated, because of limited treatment choices, there are other instances where, with early recognition and intervention, the treatment regimen can be changed to obviate the adverse effect.

HEALTH DISPARITIES

A growing body of evidence is surfacing that suggests patients of African American descent are at a significant increased risk of taxane-induced neuropathy. Data from breast cancer trials have recently put the risk of CIPN in black women at double that of white women (hazard ratio = 2.1; $P = 4.5 \times 10^{-11}$).[97] This evidence has also been supported in a retrospective cohort[98] study of 260 women (27% black) receiving paclitaxel for nonmetastatic breast cancer. Black race was the only statistically significant independent risk factor for dose-limiting CIPN. Compared with whites, black women had a greater than 3-fold increased risk of dose-limiting CIPN (hazard ratio = 3.35; 95% CI, 1.54 to 7.28). Clinicians need to be made aware of such emerging data supporting racial differences in susceptibility, onset, and severity in order to allow for appropriate management strategies and continued adherence to crucial chemotherapy treatments.[98]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have 2 or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care.[99] In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients in order to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any management plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making around guideline use and implementation. Indeed, cancer survivors with pre-existing conditions may be predisposed or more vulnerable to the development of neuropathy. Conditions reported to be associated with an increased risk include diabetes, alcoholism, nonalcoholic liver disease, amyloidosis, HIV, peripheral vascular disease, and nutritional deficiencies.[77,100] Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

Taking the above considerations into account, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and cancer survivors, and also to provide adequate services in the face of limited resources. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will

be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

LIMITATION OF THE RESEARCH AND FUTURE DIRECTIONS

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. The development of a comprehensive and standardized approach to the assessment of CIPN is still necessary to ensure the reliable and valid acquisition of data, will which allow clinicians to better recognize, understand, and respond to CIPN. Furthermore, since most studies tested interventions for paclitaxel- or oxaliplatin-induced CIPN, large, methodologically rigorous trials evaluating the prevention and treatment of CIPN caused by other neurotoxic drugs (eg, bortezomib, vinca alkaloids, *nab*-paclitaxel, docetaxel, cisplatin, thalidomide/lenalidomide) are still needed to ensure availability of evidence on which future clinical decisions can be based. Finally, many of the studies reviewed did not consistently report the adverse effects of the tested agents (see Data Supplement for Table 5: Data on Adverse Events). This is an important missing component that is indispensable for both physicians and patients in making informed decisions about management of CIPN and should be reported in all future trials.

ADDITIONAL RESOURCES

Additional Information including data supplements, evidence tables, and clinical tools and resources can be found at http://www.asco.org/guidelines/neuropathy. Patient information is available there and at www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Guide for Rating Recommendations and Strength of Evidence

Parameter	Definition
Type of recommendation	
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement.
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.
Rating for strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (eg, benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation. Furthermore, the balance of benefits versus harms substantially favors the benefits and most patients would want the intervention.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (eg, benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. Most patients would want the intervention, but many would not.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (eg, benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation. Some patients would want the intervention, some would not. Shared decision-making that incorporates benefits and risks is necessary.
Rating for strength of evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect however it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.
Inconclusive	There is conflicting evidence of effectiveness and further research is needed to inform the topic.

Table A2. Expert Panel Membership

Member	Affiliation
Charles Loprinzi, MD (Co-chair), medical oncology	Mayo Clinic
Dawn Hershman, MD (Co-Chair), medical oncology	Columbia University Medical Centre
Maryam Lustberg, MD, medical oncology	Ohio State University
Tom Smith, MD, medical oncology	Johns Hopkins
Nina Wagner-Johnston, MD, medical oncology	Washington University
Judith Paice, PhD, nursing	Northwestern University
Ellen Smith, PhD, nursing	University of Michigan
Robert H. Dworkin, PhD, pain research	University of Rochester
Bryan Schneider , MD, medical oncology, genetics	Melvin and Bren Simon Cancer Center, Indiana University
Jonathan Bleeker, MD, oncology	Mayo Clinic
Shelby Terstriep, MD, oncology	Sanford Roger Maris Cancer Center
Guido Cavaletti, MD, neurology	University of Milano-Bicocca, Italy
Patrick Gavin, RPh, Alliance patient advocate/pharmacist	Patrick Gavin R.Ph. Consulting LLC
Cynthia Chauhan, patient advocate	The Mayo Clinic Breast SPORE
Mary Lou Smith, patient advocate	Research Advocacy Network
Antoinette Lavino, RPh., BCOP, oncology pharmacist, PGIN member	Massachusetts General North Shore Cancer Center Massachusetts

NOTE. Staff: Christina Lacchetti, MHSc, and Kate Bak, MSc, Practice Guidelines Specialists, American Society of Clinical Oncology.

Table A3. Literature Search Strategy

	Search Strategy
1	exp Neoplasms/(5517150)
2	cancer$.mp. (2892023)
3	or/1-2 (5917802)
4	neuropath$.mp. (283232)
5	CIPN.mp. (258)
6	or/4-5 (283246)
7	3 and 6 (46,425)
8	(randomized controlled trial or controlled clinical trial or clinical trial).pt. (627101)
9	(meta-analysis or meta analysis or meta-analyses or meta analyses or meta-analyzed or meta-analysed or systematic-review).pt. (39,407)
10	or/8-9 (665901)
11	7 and 10 (1454)
12	(letter or editorial or comment$).pt. (2422407)
13	(case review or case report or case series).ti. (333931)
14	(infant or child or children or adolescent or pediatric or peadiatric).ti. (1246702)
15	(diabetic$ or diabetes or arthritis or stem cell).ti. (715227)
16	or/12-15 (4573330)
17	11 not 16 (1397)
18	limit 17 to english language (1334)
19	limit 18 to human [Limit not valid in AMED; records were retained] (1333)
20	limit 19 to yr = "1990 -Current" (1278)
21	limit 20 to humans [Limit not valid in AMED; records were retained] (1278)
22	remove duplicates from 21 (1252)

NOTE. Database: Ovid MEDLINE (1946 to April Week 2 2013), EMBASE (1980 to 2013 wk 16), AMED (Allied and Complementary Medicine; 1985 to April 2013).

Table A4. Definitions for Rating Potential for Risk of Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low	No major features in the study that risk biased results and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis, and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.