Pain Physician 2018; 21:571-592 • ISSN 1533-3159

Systematic Review

Treatment of Chemotherapy-Induced Peripheral Neuropathy: Systematic Review and Recommendations

Saiyun Hou, MD, PhD[1], Billy Huh, MD, PhD[1], Hee Kee Kim, PhD[1], Kyung-Hoon Kim, MD, PhD[2], and Salahadin Abdi, MD, PhD[1]

From: [1]Department of Pain Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030
[2]Pusan National University, Pusan, S. Korea

Address Correspondence:
Salahadin Abdi, MD, PhD
Department of Pain Medicine
The University of Texas MD Anderson Cancer Center
1400 Holcombe Blvd, Unit 0409
Houston, TX 77030'
E-mail: sabdi@mdanderson.org

Disclaimer: See P. 589
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-10-2018
Revised manuscript received: 06-14-2018
Accepted for publication: 07-19-2018

Free full manuscript: www.painphysicianjournal.com

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a commonly encountered disease entity following chemotherapy for cancer treatment. Although only duloxetine is recommended by the American Society of Clinical Oncology (ASCO) for the treatment of CIPN in 2014, the evidence of the clinical outcome for new pharmaceutic therapies and non-pharmaceutic treatments has not been clearly determined.

Objective: To provide a comprehensive review and evidence-based recommendations on the treatment of CIPN.

Study Design: A systematic review of each treatment regimen in patients with CIPN.

Methods: The literature on the treatment of CIPN published from 1990 to 2017 was searched and reviewed. The 2011 American Academy of Neurology Clinical Practice Guidelines Process Manual was used to grade the evidence and risk of bias. We reviewed and updated the recommendations of the ASCO in 2014, and evaluated new approaches for treating CIPN.

Results: A total of 26 treatment options in 35 studies were identified. Among these, 7 successful RCTs, 6 failed RCTs, 18 prospective studies, and 4 retrospective studies were included. The included studies examined not only pharmacologic therapy but also other modalities, including laser therapy, scrambler therapy, magnetic field therapy and acupuncture, etc. Most of the included studies had small sample sizes, and short follow-up periods. Primary outcome measures were highly variable across the included studies. No studies were prematurely closed owing to its adverse effects.

Limitations: The limitations of this systematic review included relatively poor homogeneous, with variations in timing of treatment, primary outcomes, and chemotherapeutic agents used.

Conclusion: The evidence is considered of moderate benefit for duloxetine. Photobiomodulation, known as low level laser therapy, is considered of moderate benefit based on the evidence review. Evidence did not support the use of lamotrigine and topical KA (4% ketamine and 2% amitriptyline). The evidence for tricyclic antidepressants was inconclusive as amitriptyline showed no benefit but nortriptyline had insufficient evidence. Further research on CIPN treatment is needed with larger sample sizes, long-term follow-up, standardized outcome measurements, and standardized treatment timing.

Key words: Chemotherapy-induced neuropathy, peripheral neuropathy, chemotherapy-tumor, neuropathic pain, chronic pain, toxicology, treatment, reduction of pain, level of evidence.

Pain Physician 2018: 21:571-592

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of neurotoxic chemotherapeutic agents such as taxanes, vinca alkaloids, platinum compounds, bortezomib, and thalidomide. CIPN is mainly involved in a sensory peripheral neuropathy though some patients experience motor symptoms such as weakness and autonomic neuropathy (1). The sensory neuropathy is

often distributed in a "stocking and glove" manner, causing symptoms such as pain, allodynia, loss of sensation, paresthesia, numbness, tingling, and gait disturbance (2,3). CIPN can cause significant loss of functional abilities and negatively affect quality of life, which can lead to dose reductions, discontinuation of treatment, and ultimately affect overall survival (2). CIPN has dose limiting side effect that likely will increase in prevalence as new cancer therapies extend patient survival times. One study established the prevalence of CIPN at 68.1% in the first month after chemotherapy, 60.0% at 3 months, and 30.0% at 6 months or more (1). Some chemotherapy drugs were associated with even higher prevalence and duration of CIPN. For instance, approximately 80% of patients who received taxanes and oxaliplatin therapy continue to suffer from CIPN even 6 months or 2 years after chemotherapy (4-6).

At present, no sufficient treatment options are available for CIPN and its exact pathophysiology is not clear. CIPN is most commonly considered as neuropathic pain due to axonopathy by dying back axonal degeneration (7). However, most of the pharmacologic treatments for neuropathic pain including tricyclic antidepressants, and anticonvulsants, are minimally effective in CIPN or have unacceptable side effects (8-11). Therefore, the mechanisms underlying CIPN may differ from those involved in typical neuropathic pain conditions.

To date only duloxetine is recommended by the American Society of Clinical Oncology (ASCO) for the treatment of CIPN, on the bases of a modest positive result in 1 randomized control trial (RCT) (12). In addition, several systemic reviews (12-15) evaluating strategies for the prevention and treatment of CIPN have been recently published; however these reviews focus only on pharmacologic treatments of CIPN and were mainly limited to RCTs. Here we performed the evaluation of all selected studies, not only of pharmacologic treatments, but also of non-pharmacologic treatment modalities. The goals of this systematic review were to 1) provide a comprehensive systematic review for all available treatments for CIPN; 2) evaluate the strengths and weaknesses of each study; and 3) summarize the level of evidence and provide evidence-based recommendations.

Methods

The methodology used in this systematic review followed the procedures for systematic reviews of therapeutic questions in the 2011 American Academy of Neurology (AAN) *Clinical Practice Guideline Process Manual* (16,17). We chose to use the *AAN Clinical Practice Guideline Process Manual* for this review because it formed the basis of 45 evidence-based reviews published by the AAN and made available on the Agency for Healthcare Research and Quality's National Guideline Clearinghouse (www.guideline.gov), a public resource for evidence-based clinical practice guidelines (16-18). It has been widely used by many authors (19-22).

Criteria for Considering Studies for this Review

Types of Studies

RCTs and prospective non-randomized, case-control, cohort, and cross-over studies, and retrospective studies published in English from January, 1990 to September, 2017 were included. Case reports, case series, abstracts, book chapter, and review articles, letters to the editor, and newspaper articles were excluded. Animal studies and studies of children were also excluded.

Types of Participants

Patients of interest were adults with CIPN of at least 18 years of age.

Types of Interventions

Studies evaluating any treatment modality, including pharmacologic and non-pharmacologic modalities, were included.

Types of Outcome Measures

Outcome measures are variable in all selected studies so that the uses of specific outcome measures were not inclusion criteria. Here we mainly focus on pain relief and the change in severity of neuropathic symptoms as the primary outcome parameter.

Literature Search

All of the available trials or studies in any language from any country describing appropriate management of CIPN with outcome evaluations were considered for inclusion. We searched Pubmed, Scopus, the Cochrane Library, and ClinicalTrials.gov for studies published from January 1990 through September 2017.

The search strategy was designed to identify studies of the treatment of CIPN. The search terms included: "chemotherapy," "peripheral neuropathy," "neuro-

pathic pain," "treatment," and "cancer." Different combinations of the search terms were made by using the Boolean operators "AND," "OR," and "NOT."

Data Extraction

Two review authors working independently, in a non-blinded standardized manner, searched for relevant literature, and extracted the data from the included studies. Disagreements were resolved by discussion between the 2 authors; if no agreement could be reached, another resolved the dispute.

Analysis of Evidence

The quality of the included studies' evidence was analyzed using the methods described in the 2011 AAN *Clinical Practice Guideline Process Manual* (16,17). Studies were first classified on the basis of the strength of the evidence they presented into 4 levels ranging from the strongest, Class I, to the weakest, Class IV (Table 1). The level of confidence in the evidence was determined using 4 levels of confidence, as described in the 2011 AAN *Clinical Practice Guideline Process Manual* (Table 2). Level of confidence in evidence is initially

Table 1. *Rating scheme for the strength of evidence for therapeutic questions.*

Class I	Randomized, controlled clinical trial (RCT) in a representation population Masked or objective outcome assessment Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences Also required: Concealed allocation No more than 2 primary outcomes specified Exclusion/inclusion criteria clearly defined Adequate accounting for dropouts (with at least 80 percent of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias For noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs, the following are also required * The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective) The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment The interpretation of the study results is based on a peer-protocol analysis that accounts for dropouts or crossovers. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate
Class II	An RCT that lacks 1 or 2 criteria a-e (see Class I) or a cohort study meeting criteria b-e (see Class I) Randomized, crossover trial missing 1 of the following 2 criteria: Period and carryover effects described Baseline characteristics of treatment order groups presented All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences Masked or objective outcome assessment
Class III	Controlled studies (including studies with external controls such as well-defined natural history controls) Crossover trial missing both of the following 2 criteria: Period and carryover effects Baseline characteristics presented A description of major confounding differences between treatment groups that could affect outcome ** Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team
Class IV	Did not include patients with the disease Did not include patients receiving different interventions Undefined or unaccepted interventions or outcome measures No measures of effectiveness or statistical precision presented or calculable

*Numbers 1–3 in Class I are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III

**Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data) .

anchored to class of evidence; then considering various factors that can downgrade or upgrade confidence in evidence, which was described previously (16,17).

The strength of the recommendations for use of the therapeutic modalities was determined on basis of the level of confidence in the evidence. Recommendation strength was stratified into 4 levels: A, clinicians must or must not offer the treatment; B, clinicians should or should not offer the treatment; C, clinicians may or may not offer the treatment; and U, no recommendation (Table 3) (16,17). Other factors that affected the recommendation strength included: the generalizability of the study, the clinical importance of the treatment's effect, the risk of harm weighed against the benefit of the treatment, the treatment availability and cost, and the alternative interventions.

Results

Search Results

A total of 1,288 relevant studies were identified by the literature search. Of these, 117 studies were examined in detail and a total of 35 studies ultimately met all inclusion criteria (3,8-11,23-52). The included studies described total 26 treatment options for CIPN, including pharmacological therapy, light therapy, scrambler therapy, magnetic field therapy, acupuncture, dietary therapy and long-wave diathermy therapy, etc. Among included studies, 7 successful RCTs, 6 failed RCTs, 18 prospective studies, and 4 retrospective studies were identified (Fig. 1).

Quality Assessment

Table 4 described the results of each study reviewed. The strengths and weaknesses of each study were evaluated and quality assessment is summarized in Table 5. On the basis of the AAN criteria, the level of confidence in the evidence was determined for each treatment options. But there are various factors that can downgrade (e.g., power) or upgrade confidence in evidence (16,17). Based on the strengths and weaknesses for each study, the level of confidence in evidence for each treatment option was summarized in Table 6. Among 7 successful RCTs, duloxetine had Class II level of strength of evidence and photobiomodulation had Class I, but downgraded to Class II due to relative small sample size. The remaining 5 studies were identified as 2 Class IV and 3 Class II initially, then downgraded to very low level of confidence in evidence due to poor design quality. In 6 failed RCTs, 2 Class II large sample size studies with treatment of lamotrigine, and topical 2% amitriptylin/ 4% ketamine showed negative outcome. Other studies presented with poor design quality with Class IV evidence level.

Recommendations

The strength of the recommendation for each treatment option is shown in Table 6. The majority of treatments were considered level U (no recommendation) on the basis of a paucity of high-quality and consistent evidence. No recommendation can be made for the following treatments:

1. Acetyl-L-carnitine (ALC)
2. Amitriptyline

Table 2. *Level of confidence in evidence.*

- High confidence corresponds to a "highly likely" conclusion; anchor is 2 Class I studies
- Moderate confidence corresponds to "likely" conclusion; anchor is 1 Class I study or 2 Class II studies
- Low Confidence corresponds to "possibly" conclusion; anchor is 1 Class II study, or 2 Class III studies
- Very low confidence corresponds to "insufficient" conclusion; anchor is < 2 Class III

Table 3. *Rating scheme for the strength of the recommendations.*

Classification of recommendations	
Level A	Strongest recommendation, and is denoted by "must" or "must not"; based on high confidence in the evidence, and high magnitude of benefit and low risk; "must" recommendations are relatively rare
Level B	"Should" or "should not"; tend to be more common than A, since requirements are less stringent but still based on moderate evidence and risk/benefit profile
Level C	"May" or "may not"; lowest allowable recommendation
Level U	No recommendation can be made because of insufficient evidence

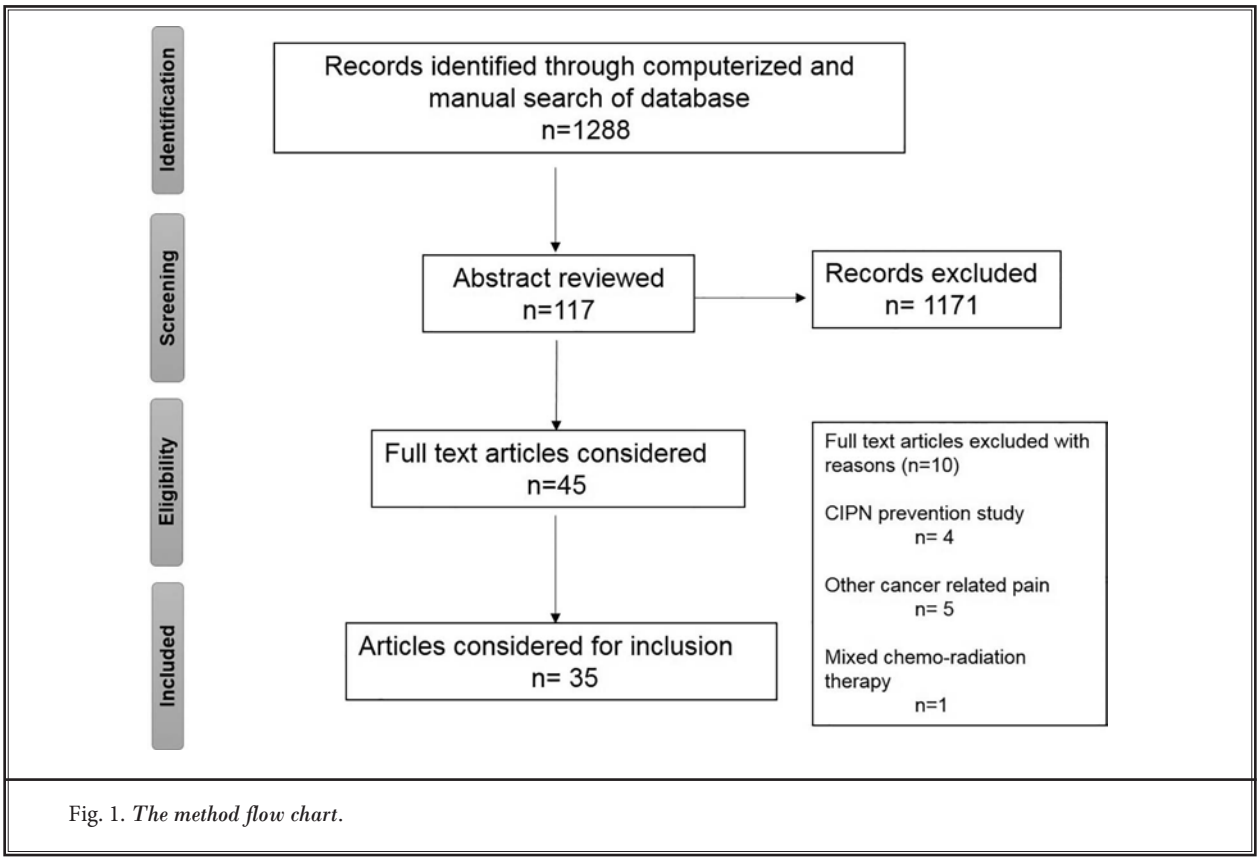

Fig. 1. *The method flow chart.*

3. Cannabinoids
4. Gabapentin
5. Intravenous lidocaine
6. Neurofeedback (NFB)
7. Nortriptyline
8. Alpha lipoic acid, methylsulfonylmethane, and bromelain dietary supplement (OPERA)
9. Oxycodone (long-acting)
10. Palmitoylethanolamide (PEA)
11. Venlafaxine
12. Topical baclofen, amitriptyline and ketamine (BAK-PLO)
13. Topical menthol (TRPM8 agonist)
14. Acupuncture
15. Acupuncture like transcutaneous nerve stimulation (ALTENS)
16. Electro-acupuncture
17. Laser acupuncture (LA)
18. Percutaneous auricular neurostimulation (PANS)
19. Sweet bee venom pharmacopuncture (SBVP)
20. Interferential therapy and long-wave diathermy at high power (ITH)
21. Low-frequency magnetic field therapy
22. Scrambler therapy

Lamotrigine and topical KA (4% ketamine and 2% amitriptyline) should not be offered by physicians for treating CIPN, as they appear to have no benefit even in a large RCT study and many severe adverse events (AEs) in topical KA (35).

To date, only Duloxetine and photobiomodulation (PBM) can be considered to provide a modest benefit for patients with CIPN. Physicians may offer them for patients with cancer experiencing CIPN. PBM, a low level laser therapy, showed significant improvement in modified total neuropathy score (mTNS) at 8 weeks. Although this was a high-quality study with consistent evidence, we downgraded to the low level of confidence in evidence (from moderate to low level) because the sample sizes appeared inadequate, and all the patients recruited were female. Therefore, we consider the evidence to show only modest symptom improvement with PBM for patients with CIPN at 8 weeks.

Table 4. *Summary of the studies regarding the treatment of CIPN.*

Treatment	Author	Study design	Neurotoxic chemotherapy agent	Sample size	Intervention dose	Intervention entry	Outcome measures	Data collection	Follow-up
IV infusion Acetyl-L-carnitine (ALC)	Maestri 2005 (23)	Prospective, non-control	Paclitaxel, cisplatin or both	27 total	ALC 1g/die IV daily for at least 10days (range 10-20)	At least 1 mon after completion of chemotherapy	Severity of neuropathy by WHO toxicity grading list. AEs	Baseline and end of treatment	End of treatment. (at least 10 days).
Amitriptyline	Kautio 2008 (8)	RCT failed	Vinca alkaloids, Platinum derivatives, Taxanes, and combination	44 total; 17 Amitr vs. 16 PL.	Amitr 10mg daily orally for 1st week, escalate 10mg weekly up to 50mg daily if tolerated.	Patient were receiving chemotherapy	Primary: NRS, Severity of sensory and motor neuropathy by NCI-CTC Secondary: global improvement of neuropathic symptoms by VRS; QOL by EORTC OLO-C30; Anxiety by a modified state and trait anxiety inventory; Depression by EORTC OLO-C30; Neuropathic pain by NPSI. AEs	Severity of sensory and motor neuropathy at baseline and week 8. Global improvement of neuropathic symptoms at baseline, twice a week. QOL, Anxiety, depression and neuropathic pain at baseline, week 4 ad week 8.	8 weeks
Cannabinoid	Lynch 2014 (24)	RCT crossover	Cisplatin, Oxaliplatin, Paclitaxel, Vincristine, and combination	18 total; 9 Canna initially, then cross over to PL. 9 PL initially, then cross over to Canna.	Canna: start 1 spray daily, then titrate 1-2 spray daily until reach a dose to help the pain. No exceed 12 spray daily. Continue stable dose for 4 weeks. Then taper to stop. Washout: 2 weeks	At least 3 mons after completion of chemotherapy	Primary: NRS Secondary: SF-36; QST for sensory testing; AEs	Baseline, week 2 and week 4.	4 weeks. 10 patients chose to continue at 3 and 6 months.
Duloxetine	Smith 2013 (25)	RCT crossover	Paclitaxel, other taxane, oxaliplatin	231 total; Group A: 85, Dulox then cross over to placebo; Group B: 93, placebo then cross over to Dulcox	30mg daily orally for 1st week and 60mg daily for 4 additional weeks; 2 weeks washout peirod	At least 3 mons after completion of chemotherapy	Primary: average pain by BPI Secondary: BPI, QOL (FACT/GOG-Ntx) AEs by NCI-CTCAE	Baseline and weekly	5 weeks
	Yang 2012 (26)	Prospective non-controlled	Oxaliplatin	39 Dulox	30mg daily orally initially escalated to 60mg daily for total 12 weeks	Patient had received chemotherapy	Pain: VAS score AEs by NCI-CTCAE	Baseline and 12 weeks	12 weeks
	Hirayama 2015 (27)	RCT crossover	Paclitaxel, Oxaliplatin, Vincristine, bortezomib	34 total; Group A 17: Dulox then crossover to Vitamin B12; Group B 17: Vitamin B12 then crossover to Dulox	Dulox: 20mg daily orally for 1st week, and 40mg daily for 3 additional weeks. Vitamin B12: 1.5mg oral daily for 4 weeks; 2-4 weeks washout period	Patient were receiving and had received chemotherapy	Primary: Change of pain and numbness by VAS score Secondary: AEs by NCI-CTCAE	Baseline and weekly	4 weeks
	Otake 2015 (28)	Retrospective	Paclitaxel	25 total	18 patients: Dulox 20mg daily orally 7 patients: Dulox 40mg daily orally	unclear	Severity of pain and numbness by NCI-CTCAE AEs	NR	NR

Table 4 (cont.. *Summary of the studies regarding the treatment of CIPN.*

Treatment	Author	Study design	Neurotoxic chemotherapy agent	Sample size	Intervention dose	Intervention entry	Outcome measures	Data collection	Follow-up
Gabapentin	Tsavaris 2008 (11)	Prospective pilot study	Eirubicin, Docetaxel, Paclitaxel, Ifosfamide, Vinorelbin, Gemcitabine, Cisplatin, Carboplatin, Oxaliplatin, Leucovorin, Fluorouracil and Doxorubicin	110 total; 75 Gaba vs. 35 control	Gaba: 800mg bedtime orally Control: fixed dose of naproxen and codeine/ paracetamol.	unclear	Primary: change of analgesic response by patient-answered questionnaire Secondary: AEs	3-15wks depends on response	15 weeks
	Rao 2007 (10)	RCT phase 3 crossover	Vinca alkaloids, Taxanes, Platinum-based compounds or combination	115 total; Gaba 57, then cross over to PL, PL 58, then cross over to Gaba.	Gaba: 300mg daily orally initial dose, escalate over 3 weeks to a target dose of 2700mg daily Washout: 2 weeks	Patient were receiving and had received chemotherapy	Primary: average pain by NRS or ENS. Secondary: 1. CIPN-related symptoms by WHO scale; 2. short form McGill Pain Questionnaire; 3. BPI-short form; 4. SGI; 5. Symptom distress scale; 6.POMS; 7. QOL uniscale; 8. AEs	Primary outcome and AEs: Baseline and weekly until week 6. Secondary outcome: baseline, week 6, 8 and 14.	Each arm 6 weeks and washout 2 weeks. Total 14 weeks.
Lamotrigine	Rao 2008 (9)	RCT phase 3	Vinca alkaloids, Taxanes, Platinum-based compounds or combination	131 total; Lamo 63 vs. PL 62.	Lamo: 25mg bedtime orally x2 weeks, 25mg BID x 2weeks, 50mg BID x 2 weeks, 100mg BID x 2weeks, 150mg BIDx 2 weeks. Then tapering off over 4 weeks.	Patient were receiving and had received chemotherapy	Primary: Average pain by NRS, ECOG, or ENS. Secondary: 1. CIPN-related symptoms by WHO scale; 2. Short form McGill Pain Questionnaire; 3. BPI-short form; 4. SGI; 5. Symptom distress scale; 6.POMS; 7. QOL uniscale; 8. AEs by NCI-CTC	Primary outcome and AEs: baseline and weekly. Secondary outcome: baseline and biweekly	10 weeks
IV infusion Lidocaine	Van Den Heuvel 2017 (3)	Prospective study	Oxaliplatin, capecitabine, cisplatinum, docetaxel, cydophosphamide, trastuzumab, pfludarabine, paclitaxel, etoposide.	9 total	Lidocaine: 1.5mg/kg IV in 10 mins followed by 1.5mg/kg/h over 5 hours.	At least 3 mons after completion of chemotherapy	Pain score by NRS Pain sensitivity and sensory changes by pressure pain thresholds, mechanical and thermal sensory testing.	Baseline and every 15 mins during 1st hour, every 30 mins until the end of infusion, then 3 times daily for 14 days, weekly for every 3 weeks.	Mean 23 days (3 – 56 days)
Neurofeedback (NFB)	Prinsloo 2017 (50)	RCT	Paclitaxel, Oxaliplatin, other Taxane, other platinum or combination	71 total; 30 NFB vs. 32 control.	NFB: 20 sessions over 10 weeks. Control: wait-list control.	At least 3 mons after completion of chemotherapy	Primary: BPI worst pain item Secondary: BPI, deep pain by PQAS and EEGs	Baseline and 10 weeks	10 weeks

Table 4 (cont.. *Summary of the studies regarding the treatment of CIPN.*

Treatment	Author	Study design	Neurotoxic chemotherapy agent	Sample size	Intervention dose	Intervention entry	Outcome measures	Data collection	Follow-up
Nortriptyline	Hammack 2002 (29)	RCT crossover	Cisplatinum	51 total; 26 Nortrip initial, then cross over to PL; 25 PL initial, then cross over to Nortrip	Nortrip: 25mg daily orally, then 25mg additional titrate weekly as tolerated. The target maximum dose at the end of each drug phase was 100mg.	Patient were receiving and had received chemotherapy	Primary: change in the pain/ paresthesiae severity by VDS and change of daily activity. Secondary: change in pain score by VAS; hours of sleep, QOL, Preference and AEs	Baseline and weekly	Each arm 4 weeks and washout 1 week, total 9 weeks.
OPERA® (new dietary supplement)	Desideri 2017 (30)	Prospective, non-control study	Platins, Vinca alkaloid, Taxanes, Eribuline	25 total	OPERA® (new dietary supplement) one capsule daily orally, including á-lipoic acid, Boswellia Serrata, methylsulfonylmethane and bromelain	Patient were receiving and had received chemotherapy	Primary: change of VAS and CIPN by NCI-CTC, mISS , and TNSc. Secondary: neuropathy reduction at 12 weeks and AEs by NCI-CTC	Baseline, every 3 weeks	12 weeks
Oxycodone (long acting)	Cartoni 2012 (31)	Prospective, open label. Non- control study	Bortezomib	46 total	Oxycodone: starting with 10mg q12h orally, then titrate with 20mg, 40mg q12h to a maximum dose of 80mg q12h daily over 14 days	Patient were receiving chemotherapy	Primary: pain intensity by NRS, BP Secondary: daily function, safety and AEs by NCI-CTC	Baseline and day 3,7 and 14	14 days
Palmitoylethanolamide (PEA) an endogenous fatty acid amide	Truini 2011 (32)	Prospective, non- control study	Bortezomib, Thalidomide	20 total	PEA: 300mg BID orally	unclear	Pain and warmth thresholds, nerve fibre function by laser stimulus, motor and sensory nerve conduction study by EMG.	Baseline and 2 mons	2 mons
Photobiomodulation (PBM)- laser therapy	Argenta 2017 (33)	RCT	Taxane, Platinum or both	70 total; 30 PBM, 40 sham-group, then crossover to PBM+PT	3 times per week for 6 weeks	At least 1 mon after completion of chemotherapy	Primary: reduction in neuropathy measured by mTNS. Secondary: time to onset of treatment effect, time to maximum effect, durability of response, and response to addition of PT to PBM.	Baseline and 4,8,16 weeks following initiation of treatment	16 weeks
Venlafaxine	Kus 2016 (34)	Retrospective control study	Taxane, oxaliplatin	206 total; 91 Venla vs 115 control.	Venla XR 75mg daily orally	Patient were receiving and had received chemotherapy	1. Pain intensity, neuropathic pain symptom inventory scale (NPSI) 2. AEs by NCI-CTCAE	Baseline and every 3 weeks	9weeks
Topical 2% amitriptyline and 4% ketamine	Gewandter 2014 (35)	Phase III RCT	Taxane or non taxane	462 total; 229 KA and 233 PL.	KA: up to 4g two times daily to each area with pain, numbness and tingling	At least 1 mon after completion of chemotherapy	Primary: average score of pain, numbness and tingling by NRS at week 6. Secondary: worst pain, AEs by NCI-CTC	Baseline and week 3 and 6.	6 weeks
Topical baclofen, amitriptyline and ketamine (BAK-PLO)	Barton 2011 (36)	RCT	Vinca alkaloids, oxaliplatin, cisplatin, taxanes, thalidomide or others	208 total; 101 BAK and 102 PL.	BAK: 1.31g of a compounded gel containing 10mg of baclofen, 40mg of amitriptyline and 20mg ketamine.	Patient were receiving and had received chemotherapy	Primary: changes in the sensory subscale by EORTC QLQ-CIPN20. Secondary: POMS, BPI, sensory subsection of NCI-CTC and AEs	Baseline and week 4	4 weeks

Table 4 (cont.. *Summary of the studies regarding the treatment of CIPN.*

Treatment	Author	Study design	Neurotoxic chemotherapy agent	Sample size	Intervention dose	Intervention entry	Outcome measures	Data collection	Follow-up
Topical methol (TRPM8 agonist)	Fallon 2015 (37)	Prospective, non-control study	Oxaliplatin, paclitaxel, taxotere, bortezomib, cisplatin and carboplatin	51 total. 38 completed and evaluated	Topical methol: 1% in aqueous cream	8-24 mons after completion of chemotherapy	Primary: BPI Secondary: HADS, PCS, LANSS, QST, Objectively measured walking ability and hand dexterity	Baseline and week 2,4 and 6	6 weeks
Acupuncture	Bao 2014 (38)	Prospective, non-control study	Bortezomib	27 total	Acupuncture: bilateral ear points, upper and lower extremities point. Total 10 sessions: twice weekly for 2 weeks, weekly for 4 weeks, the biweekly for 4 weeks.	5-178 mons after completion of chemotherapy	Primary: feasibility and safety of acupuncture Secondary: Total Neuropathy Score (TNSc) (FACT/GOG-Ntx) questionnaire Neuropathy Pain Scale (NPS), NCS. Serial serum levels of proinflammatory and neurotrophic cytokines	Baseline and week 1, 2,3,4,5,6,8,10 and 14.	14 weeks
	Schroeder 2012 (39)	Prospective, non-randomized study	Docetaxel, doxorubicin, cyclophosphamide, oxsliplatin, cisplatin, rituximab, fludarabin	11 total; 6 acupunture, 5 control	Acupuncture: 10 consecutive weeks	At least 1 year after completion of chemotherapy	NCS	Baseline and 6 mons	6 mons
	Donald 2011 (40)	Retrospective study	Bortezomib, vincristine, thalidomide, oxaliplatin, docetaxel, paclitaxel and carboplatin	18 total	Acupuncture: 6 weekly sessions	unclear	Outcomes: symptoms change, relaxation, reduced stress, better sleep, improved mood, less pain medication AE: NR	Baseline and week 6	6 weeks
Electro-acupuncture	Garcia 2014 (41)	Prospective, non-control study	Bortezomib, thalidomide	27 total	Electro-acupunture: 3 times a week for 4 weeks, one week off, then switch to 2 times a week for additional 4 weeks. Total 9 weeks	0.75-41.5 mons after completion of chemotherapy	Primary: FACT/GOG/NTX Secondary: BPI-SF, Timed function test, Balance test, NCS.	Baseline, week 4, 9 and 13.	13 weeks
Laser acupuncture (LA)	Hsieh 2016 (42)	Prospective, non-control study	Oxaliplatin	17 total	LA: 3 times per week for 4 weeks.	2.32±1.05 years after completion of chemotherapy	Primary: The pain quality assessment scale (PQAS) chemotherapy-induced neurotoxicity questionnaire (CINQ) Secondary: oxaliplatin-specific neurotoxicity scale (OSNS) quantitative touch-detection threshold (using von Frey filaments) cold-triggered pain withdrawal latency (using the cold-water immersion test) AEs.	Baseline and week 4.	4 weeks

Table 4 (cont.. *Summary of the studies regarding the treatment of CIPN.*

Treatment	Author	Study design	Neurotoxic chemotherapy agent	Sample size	Intervention dose	Intervention entry	Outcome measures	Data collection	Follow-up
Percutaneous auricular neurostimulation (PANS)	Sacco 2016 (51)	Retrospective study	NR	18 for pain score evaluation; 32 for qualitative functional outcome evaluation	PANS: intermittent stimulation on 3 points on each ear for 4 days, then evaluation. Place a second device if positive response	unclear	Pain score by nonparametric tests Functional outcomes by a qualitative content analysis.	Baseline and after 2-7 (Mean 4.5) treatments	2-7 treatments
Acupuncture like transcutaneous nerve stimulation (ALTENS)	Wong 2016 (52)	Prospective study	Oxaliplatin, fluorouracil, eribitux, doxorubicin, cydophosphamide, paclitaxel, trastuzumab, carboplatinum, taxol, cisplatinum, vinorelbine, docetaxel, capecitabine, patupolone and methotrexate	40 total; 27 ALTENS, 13 Acupuncture	ALTENS: twice weekly for 12 treatments over 6-8 weeks. Acupuncture: twice weekly for 12 treatments over 6-8 weeks.	At least 2 mons after completion of chemotherapy	Primary: mTNS at 6 mons Secondary: mTNS, numbness score, ESAS, AEs.	Baseline, treatment completion, 3 and 6 mons after tx.	6 mons
Sweet bee venom pharmacopuncture (SBVP)	Yoon 2012 (43)	Prospective, non-control study	Taxanes, cisplatin, carboplatin or oxaliplatin	11 total	SBVP: 0.1ml SBVP was injected into 4 acupuncture points. 6 treatments over 3 weeks.	At least 1 mon after completion of chemotherapy	Primary: World Health Organization Common Toxicity Criteria for Peripheral neuropathy (WHO grading system) Secondary: VAS, PNQ, HRQOL AEs by NCI-CTCAE	Baseline, post 2nd, 4th and 6th treatment and 3 weeks after final treatment	6 weeks
Interferential therapy and long-wave diathermy at high power (ITH)	Lindblad 2016 (44)	RCT	Oxaliplatin, taxane, vincristine, cepecitabine, cisplatin and vinblastine	67 total; 34 ITH vs 33 for LDL (Long-wave diathermy at low power)	Once a week for 12 weeks	Patients had received and were receiving chemotherapy	Primary: NRS Secondary: discomfort, nerve symptoms, subjective measurement of dizziness (Dizziness Handicap Inventory), and balance AE: NR	Baseline, week 12 and week 37	37 weeks
Low frequency magnetic field therapy (MEF)	Geiger 2015 (45)	Prospective non-control study	Cisplatin, oxaliplatin, paclitaxel, docetaxel, vincristine, or combination	20 total	Twice daily with 4-12 Hz for 5 mins separately for each affected extremity for 3-4 weeks	unclear	Outcome: degree of severity of CIPN by CTCAE, Quality of neuropathic pain, NCV with EMG AE: NR	Baseline and after treatment (3-4 weeks)	3-4wks.
	Rick 2017 (46)	RCT phase III	Platinum, taxane, vinca alkaloids, other	44 total; 21 MEF vs. 23 PL	Twice daily with 4-12 Hz for 5 mins separately for each affected extremity for total 3 mons.	13-1390 days (average 88 days) after completion of chemotherapy	Primary: NCV with EMG Secondary: Common Toxicity Criteria (CTCAE) score Pain detect questionnaire	Baseline, 3 weeks and 3 mons	3 mons

Table 4 (cont.. *Summary of the studies regarding the treatment of CIPN.*

Treatment	Author	Study design	Neurotoxic chemotherapy agent	Sample size	Intervention dose	Intervention entry	Outcome measures	Data collection	Follow-up
Scrambler therapy	Pachman 2015 (47)	Prospective study with non-control	Paclitaxel, carboplatin, oxaliplatin, cisplatin and vincristine.	37 total	Scrambler: daily session 30min for up to 10 days.	At least 1 mons after completion of chemotherapy	Outcome :neuropathy questionnaire, global impression of change questionnaire, vibration sensation and AEs	Baseline, daily prior to each session, then weekly after completion of treatment.	10 weeks
	Coyne 2013 (48)	Prospective, non-control study	NR	39 total; 33 CIPN, 3 post-mastectomy, 2 postherpetic neuropathy, 1 radiation related pain	45 mins daily treatment for 10 consecutive days	At least 1 mon after completion of chemotherapy	Primary outcome: NRS Secondary outcome: changes in the Brief Pain Inventory and European Organization for Treatment and Cancer QLC-CIPN-20 AE: NR	Baseline, week 2, 1 mon, 2 mons and 3 mons	3 mons
	Smith 2010 (49)	Prospective non-control study	Carboplatin, paclitaxel, docetacel. Cyclophamide, procarbazine, thalidomide, oxaliplatin, fluorouracil, leucovorin, bortezomib,	18 total.	60 mins daily treatment for 10 consecutive days	At least 1 mon after completion of chemotherapy	Primary: pain reduction by 20% by NRS Secondary: severity of CIPN, quality of life by Uniscale, change in use of pain drugs, AEs by CTEPTS.	Baseline, week1, 2 of treatment, week 4,8,12.	12 weeks

NCI-CTCAE: National Cancer Institute's Common Terminology Criteria for Adverse Events; NCI-CTC: National Cancer Institute's Common Toxicity Criteria; QOL: Quality of life; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.; NPSI: Neuropathic Pain Symptom Inventory; QST: Quantity Sensory Testing; ENS: Eastern Cooperative Oncology Group Neuropathy Scale; ECOG: Eastern Cooperative Oncology Group; VDS: Verbal descriptor scale. ; VAS: Visual Analogue Scale.; SGI: Subjective Global Impression; POMS: Profile of Mood States Short Form; mISS : Sensory Sum Score; TNSc: Total Neuropathy Score ; mTNS: Modified Total Neuropathy Score; BPI: Brief Pain Index; LEP: Laser Evoked Potential; NCS: Nerve Conduction Study; SNAP: Sensory Nerve Action Potential; CMAP: Compound Motor Action Potential; PT: Physiotherapy.; HADS: Hospital Anxiety and Depression Scale; PCS: Pain Catastrophizing Scale; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs.; QST: Quantitative Sensory Testing; FACT/GOG/Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group- Neurotoxicity; FACT/GOG/G: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group- General; Neuropathy Pain Scale (NPS); PQAS: The Pain Quality Assessment Scale; CINQ: Chemotherapy-Induced Neurotoxicity Questionnaire; OSNS: Oxaliplatin-Specific Neurotoxicity Scale; WHO grading system: World Health Organization Common Toxicity Criteria for Peripheral neuropathy; PNQ: Patient Neurotoxicity Questionnaire; HRQOL : Health-Related Quality of Life; CTEPTS: Cancer Therapy Evaluation Program Toxicity Scales; PQAS: Pain Quality Assessment Scale; ESAS: Edmonton Symptoms Assessment Score

Adverse Events

Of the included studies, 24 examined the AEs associated with treatments for CIPN. Most reported that the AEs were mild and tolerable. No studies were prematurely closed because of high toxicity. Most studies used NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) or NCI Common Toxicity Criteria (NCI-CTC) to evaluate AEs, but a few studies used the World Health Organization (WHO) Common Toxicity Criteria for peripheral neuropathy toxicity evaluation. Only 2 studies reported NCI-CTCAE Grade 3 AEs. One is the large RCT crossover study for duloxetine reporting that 16% of patients in the duloxetine group vs. 27% in the placebo group had Grade 2 AEs, and that 7% of patients in duloxetine group vs. 3% in the placebo group had Grade 3 AEs (25). Another study enrolled 46 patients with CIPN to be treated with oxycodone, 18 of these patients had mild AEs, and only 1 patient had Grade 3 AEs (31).

Discussion

This systematic review provided up-to-date evidence-based recommendations for the treatment of CIPN. We were unable to make a recommendation for 22 of the 26 examined therapeutic modalities for various reasons, including inconclusive evidence, a limited number of studies, low statistical power, flaws in trial design, and inconsistency

Table 5. *Summary of quality analysis for literatures reviewed.*

Treatment	Study	Randomized controlled trial (RCT)	Masked or objective outcome assessment	Concealed allocation	Relevant baseline characteristics are presented	Substantially equivalent between treatment groups, or appropriate statistical adjustment for difference	No more than two primary outcomes specified	Exclusion/ inclusion criteria clearly defined	Adequate accounting for dropouts (<20% drop rate)	Crossover study	
										Period and carryover effects described	Baseline characteristics of treatment order groups presented
IV infusion Acetyl-L-carnitine (ALC)	Maestri 2005 (23)	–	–	–	√	–	–	–	√	N/A	N/A
Amitriptyline	Kautio 2008 (8)	√	√	√	√	√	√	√	–	N/A	N/A
Cannabinoid	Lynch 2014 (24)	√	√	√	√	√	√	√	√	–	√
Duloxetine	Smith 2013 (25)	√	√	√	√	√	√	√	–	√	√
	Yang 2012 (26)	–	–	–	√	–	–	√	–	N/A	N/A
	Hirayama 2015 (27)	√	–	–	√	√	√	√	√	√	–
	Otake 2015 (28)	–	–	–	√	√	√	–	√	N/A	N/A
Gabapentin	Tsavaris 2008 (11)	–	–	–	√	√	√	√	√	N/A	N/A
	Rao 2007 (10)	√	√	√	√	√	√	√	–	√	√
Lamotrigine	Rao 2008 (9)	√	√	√	√	√	√	√	–	N/A	N/A
IV infusion lidocaine	Van Den Heuvel 2017 (3)	–	–	–	√	√	–	√	√	N/A	N/A
Neurofeedback (NFB)	Hammack 2002 (29)	√	–	–	√	√	√	√	√	N/A	N/A
Nortriptyline	Prinsloo 2017 (50)	√	√	–	√	√	√	√	√	√	√
OPERA* (new dietary supplement)	Desideri 2017 (30)	–	–	–	√	–	√	√	√	N/A	N/A
Oxycodone (long acting)	Cartoni 2012 (31)	–	–	–	–	–	√	√	√	N/A	N/A
Palmitoylethanolamide (PEA)	Truini 2011 (32)	–	√	–	–	–	–	√	√	N/A	N/A
Photobiomodulation (PBM)-laser light therapy	Argenta 2017 (33)	√	√	√	√	√	√	√	√	N/A	N/A
Venlafaxine	Kus 2016 (34)	–	–	–	√	√	√	√	√	N/A	N/A
Topical 2% amitriptyline and 4% ketamine	Gewandter 2014 (35)	√	√	√	√	√	√	√	–	N/A	N/A
Topical baclofen, amitriptyline and ketamine (BAK-PLO)	Barton 2011 (36)	√	√	√	√	√	√	√	–	N/A	N/A
Topical menthol (TRPM8 agonist)	Fallon 2015 (37)	–	–	–	√	–	√	√	–	N/A	N/A
Acupuncture	Bao 2014 (38)	–	–	–	√	–	√	√	–	N/A	N/A
	Schroeder 2012 (39)	–	–	–	–	–	–	√	√	N/A	N/A
	Donald 2011 (40)	–	–	–	√	–	–	–	√	N/A	N/A

Table 5 (cont.). *Summary of quality analysis for literatures reviewed.*

Treatment	Study	Randomized controlled trial (RCT)	Masked or objective outcome assessment	Concealed allocation	Relevant baseline characteristics are presented	Substantially equivalent between treatment groups, or appropriate statistical adjustment for difference	No more than two primary outcomes specified	Exclusion/ inclusion criteria clearly defined	Adequate accounting for dropouts (<20% drop rate)	Crossover study	
										Period and carryover effects described	Baseline characteristics of treatment order groups presented
Electro-acupuncture	Garcia 2014 (41)	–	–	–	√	–	√	√	–	N/A	N/A
Laser acupuncture (LA)	Hsieh 2016 (42)	–	√	–	√	–	√	√	√	N/A	N/A
Percutaneous auricular neurostimul ation (PANS)	Sacco 2016 (51)	–	–	–	–	–	–	√	–	N/A	N/A
Acupuncture like transcutaneous nerve stimulation (ALTENS)	Wong 2016 (52)	–	–	–	√	–	√	√	√	N/A	N/A
Sweet bee venom pharmacopuncture (SBVP)	Yoon 2012 (43)	–	–	–	√	–	√	√	–	N/A	N/A
Interferential therapy and long-wave diathermy at high power (ITH)	Lindblad 2016 (44)	√	√	–	√	√	√	√	–	N/A	N/A
Low frequency magnetic field therapy	Geiger 2015 (45)		–	–	√	–	–	–	√	N/A	N/A
	Rick 2017 (46)	√	√	–	√	√	√	√	–	N/A	N/A
Scrambler therapy	Pachman 2015 (47)	–	–	–	–	–	–	√	–	N/A	N/A
	Coyne 2013 (48)	–	–	–	–	–	√	√	√	N/A	N/A
	Smith 2010 (49)	–	–	–	√	√	√	√	√	N/A	N/A

√ : meet criteria —: not meet criteria N/A: non applicable

between studies. However, we were able to develop recommendations for 4 of the examined modalities: clinicians may offer duloxetine or PBM, but they should not offer lamotrigine or topical KA. To improve the confidence in the results of clinical studies, 3 aspects of study design should be standardized: primary outcome measurement, chemotherapy regimens, and the timing of treatment entry.

Primary Outcome Measurements

A primary outcome measure was reported in 26 of the total 35 studies. Primary outcome measures included pain intensity by the Numeric Rating Scale (NRS), or Neuropathy Scale (ENS), Eastern Cooperative Oncology Group (ECOG) (18 studies), severity of neuropathy by NCI-CTCAE (4 studies), TNS or mTNS (4 studies), nerve conduction study (NCS) (4 studies), the Brief Pain Inventory (BPI) pain intensity (3 studies), the Neuropathic Pain Symptom Inventory (NPSI) (1 study), and the Pain Quality Assessment Scale (PQAS) (1 study), etc. No consensus exists regarding which of these measures are the best for assessing the outcomes of CIPN treatment. CIPN is a very common side effect of cancer treatment and cancer survivors present with sensory, motor and autonomic neuropathy. Clinically most patients with CIPN have sensory neuropathy, and among these patients, pain is one of the main complaint. However, some patients may have numbness, tingling, and gait imbalance as primary complaints. A few studies reported significant improvement in neuropathy but no change in pain intensity because the enrolled patients presented with mixed symptoms of neuropathy and not all patients had pain. This lack of standardized primary outcome measurements necessitates further studies that characterize and separate CIPN- related pain from other sensory symptoms; using standard outcome measures will help to determine the best outcome measure for

Table 6. *Summary of level of evidence and recommendations*

Treatments	Study	Summary of Results	Level of Strength of Evidence	Level of Confidence in Evidence	Strength of the Recommendations	Comments
IV infusion Acetyl-L-carnitine (ALC)	Maestri 2005 (23)	73% patients showed at least one grade of improvement in the neuropathy. (P < 0.0001) AEs: No serious adverse event related to ALC. Only one patient had mild insomnia and withdrew from the study.	Class IV	Very low	Level U Insufficient	Small non-controlled prospective study with short time follow-up
Amitriptyline	Kautio 2008 (8)	No significant differences in the severity of neuropathic symptoms between Amitr and PL. Amitr improved QOL compared with PL (P = 0.038) No significant changes in the depression scale and sleep. AEs: mild. 3 patients discontinued due to side effects. 15 out of 17 Amitr patients tolerated 50mg daily.	Class II	Very low	Level U Insufficient	Negative RCT with small sample size and dropout rate >20%, consider downgrade to very low level of confidence in evidence
Cannabinoid	Lynch 2014 (24)	No significant differences in NRS score, SF-36 and QST between Canna and PL. 5/16 participants showed >2 points pain score reduction with Canna. AEs: mild and transient.	Class II	Very low	Level U Insufficient	Small sample size negative RCT, downgrade to very low level of confidence in evidence
Duloxetine	Smith 2013 (25)	Decrease in Average Pain: Dulcox first: 1.06 (0.72-1.40), PL first: 0.34 (0.01-0.66); P = 0.003, effect size: 0.513; PL second: 0.41(0.06-0.89), Dulox second: 1.42 (0.97-1.87); P = 0.002, order effect: P = 0.43 Change in QOL: Dulox first: 2.44 (0.43-4.45), PL first: 0.87 (1.09-2.82), P = 0.03; Mean difference between 2 groups: 1.58 (0.15-3), P = 0.03 AEs: 16% Dulox vs. 27% PL reported grade 2; 7% Dulox vs. 3% PL reported grade 3, no grade 4 or 5	Class II	Low	Level C Moderate for	One class II study and 3 class IV study. Recommend moderate benefit.
	Yang 2012 (26)	19 patients (63.3%) showed VAS score improvement. Among whom 9 patients showed change of grade of neuropathy and 10 patients maintained a stable grade. AEs: 9 patients discontinued due to intolerable adverse events, including dizziness/nausea, somnolence, restlessness/insomnia and urinary hesitancy.	Class IV			
	Hirayama 2015 (27)	Significant decreased VAS score in Dulox: pain (P = 0.04), numbness (P = 0.03) AEs: No AEs > grade 2 by CTCAG. 5 patients discontinued due to side effect of fatigue (2 in Dulox and 3 in Vitamin B).	Class IV			
	Otake 2015 (28)	Responder: 14 patients Non-responder: 11 patients No significant association between age, origin of the tumor, regimen and dose of chemotherapy, previous treatment with neuropathy medication, timing of treatment, and perceived effectiveness of dulox treatment. AEs: very mild and tolerated. 2 patients discontinued due to its adverse effects of somnolence.	Class IV			
Gabapentin	Tsavaris 2008 (11)	Gaba achieved a greater percentage of patients than control in complete/partial analgesic response instead of minor/no response group. (P = 0.002) AEs: 25% with mild somnolence, none discontinued the study	Class IV	Very low	Level U Insufficient	One is single negative RCT, One is non-blinded, non-controlled study with positive outcome. Consider downgrade to very low level of confidence in evidence
	Rao 2007 (10)	No significant differences in average pain and secondary outcomes between Gaba and PL. AEs: mild, no significant differences	Class II			
Lamotrigine	Van Den Heuvel 2017 (3)	No significance differences in average pain and secondary outcomes between Lamo and PL. AEs: mild, no significant differences	Class II	Low	Level C Moderate against	Large negative phase III RCT study with no efficacy.
IV infusion Lidocaine	Rao 2008 (9)	Significant improvement in pain scores (7.7 to 3.1, P = 0.01) NRS scores correlated significantly with duration of infusion. 5 patients experienced a more sustained analgesic effect, 3-56 days with a mean duration of 23 days. No changes in pressure pain threshold, thermal and mechanical sensory testing.	Class IV	Very low	Level U Insufficient	Small sample size, non-control study
Neurofeedback (NFB)	Prinsloo 2017 (50)	NFB demonstrated greater improvement than the controls on BPI worst-pain item (-2.43 vs.0.09, P = 0.001) Significant improvement on other BPI items and PQAS NFB showed more activity in the dorsolateral prefrontal cortex than control.	Class IV	Very low	Level U Insufficient	Small size, short follow-up, non- blinded, non-placebo RCT. Lack of masked or objective outcome assessment

Table 6 (cont.). *Summary of level of evidence and recommendations*

Treatments	Study	Summary of Results	Level of Strength of Evidence	Level of Confidence in Evidence	Strength of the Recommendations	Comments
Nortriptyline	Hammack 2002 (29)	Insignificant in VAS before crossover (P = 0.78) but significant after crossover (p<0.04). Significant increased hours of sleep in Nortrip (p<0.02) No significant differences in QOL, daily activity and preference of treatment between two arms. AEs: 6/51 discontinued due to AEs (2 from nortrip, 4 from PL). no major toxicity, but dry mouth, dizziness, and constipation are more common with nortrip.	Class II	Very low	Level U Insufficient	Small sample size, short time follow-up with marginal significant benefit. Downgrade to very low level of confidence in evidence.
OPERA® (new dietary supplement)	Desideri 2017 (30)	Progressive reduction in VAS score, mISS, and TNSc. no statistics conducted AEs: well tolerated, no adverse effect	Class IV	Very low	Level U Insufficient	Small sample size, non RCT study
Oxycodone (long acting)	Cartoni 2012 (31)	NRS score continues to decrease on day3,7, and 14. Overall 76.5% reduction of NRS score. Significant reduced pain on day 14, compared to baseline (p<0.002). BP reduced its frequency and intensity in 47.8% of patient (p<.01). Pain interference with daily activity decreased by 74% on day 14 compared to baseline. AEs: 18/46 patients have mild AEs, NCI-CTC Grade 3 seen in 1 patient	Class IV	Very low	Level U Insufficient	Very short duration (14 days), non-control study
Palmitoylethanolamide (PEA)	Truini 2011 (32)	Lower pain scores in PEA (p<0.002) Amplitude of foot-LEPs, sural-SNAPs, and peroneal-CMAPs, hand-LEPs, ulnar-SNAPs, ulnar-CMAPs was significant increased in PEA. No significant change in warmth thresholds in PEA compared baseline. AE: NR	Class IV	Very low	Level U Insufficient	Small sample size, non-control study
Photobiomodulation (PBM)- laser therapy	Argenta 2017 (33)	PBM had a significant reduction in change in mTNS at week 8 compared to sham. (p<0.001) No significant differences between PBM and PBM/PT at week 8. (P = 0.85) No significant change in the efficacy of PBM by taxane, platinum or both. Patient received similar benefit from PBM regardless of the reported duration of their neuropathy or the degree of neuropathy. AEs: No observed complications among PBM.	Class I	Low	Level C Moderate for	All the patients recruited are female. Sample size is not adequate. (n=30). Downgrade to low level of confidence in evidence.
Venlafaxine	Kus 2016 (34)	75% neuropathic pain relief for pins and needles in Venla 53.5% vs. 0.0% control at week 3; 58.3% at week 6 and 45.2% at week 9. (P < 0.001) AEs: mild, no grade 3-4	Class IV	Very low	Level U Insufficient	Non-randomized, non-blinded study
Topical 2% amitriptyline and 4% ketamine	Gewandter 2014 (35)	The KA treatment did not significantly reduce the pain, numbness and tingling scores at week3 and week6. Those in the taxane group did show a larger reduction of pain, numbness and tingling than those in the non-taxane group at week 6. (P < 0.042) No significant difference in mean pain between KA and PL (P = 0.4). AEs: 147 (64%) in KA and 158 (68%) in PL. 8 serious reported with 4 in each arm, 21 severe AEs with 10 in KA and 11 in PL. No significant change in AEs between KA and PL.	Class II	Low	Level B Strong against	Large negative RCT showed no benefit. but taxane subgroup showed benefit from KA.
Topical baclofen, amitriptyline and ketamine (BAK-PLO)	Barton 2011 (36)	BAK gel resulted in a trend toward more improvement in sensory neuropathy (P = 0.053) and significant improvement in motor neuropathy. (P = 0.021) No significant difference in autotomic subscale, sensory subsection by NCI-CTC, BPI or POMS between BAK and PL. AEs: mild, no significant differences.	Class II	Very low	Level U Insufficient	Consider p value is borderline. Marginally significant effect, consider downgrade to very low level of confidence in evidence
Topical menthol (TRPM8 agonist)	Fallon 2015 (37)	82% patient had an improvement in BPI after 4-6 weeks of topical methol. (P < 0.001) Significant improvement in worst pain, pain interference subscales, HADS, PCS. No significant change in LANSS, QST or objectively measured walking ability and hand dexterity. Responders had a significantly greater degree of improvement than non-responders in PCS and dominant hand dexterity.	Class IV	Very low	Level U Insufficient	Small non RCT study. Mixed cancel related pain study, not specific study for CIPN. (CIPN is 61% of enrolled patients).

Table 6 (cont.). *Summary of level of evidence and recommendations*

Treatments	Study	Summary of Results	Level of Strength of Evidence	Level of Confidence in Evidence	Strength of the Recommendations	Comments
Acupuncture	Bao 2014 (38)	No significant adverse events 77% patients completed all 10 sessions of acupuncture TNSc results were invalid and not reported. Mean FACT/GOG-Ntx, mean NPS significantly decreased at week 10 and 14. (P < 0.001). No significant change in NCS. No correlation in serum cytokines for responders vs. non-responders.	Class IV	Very low	Level U Insufficient	Small prospective cohort study. Non-controlled study
	Schroeder 2012 (39)	Acupuncture had significant improvement in mean NCV and amplitude compared to control. (P = 003, 0.02)	Class IV			Small non randomized, non blinded controlled study.
	Donald 2011 (40)	82% patients had improvement in their neuropathy symptoms. 18% with no change. 76% patients had additional benefit, such as sleeping, relax, and reduced stress, improved mood.	Class IV			Small retrospective study with no control of variables.
Electro-acupuncture	Garcia 2014 (41)	Significant improvement in FACT/GOG/NTX, mean BPI at week 4,9, and 13. Significant improvement in FACT-G at week 9 and 13. No improvements were seen in social/family, emotional, or functional well-being. Significant improvement in timed-function test scores from baseline to one month follow-up. No improvement in fall risk. No significant changes in NCS. AEs: no serious adverse events reported. One patient had a worsening peripheral neuropathy symptoms during study	Class IV	Very low	Level U Insufficient	Small non-randomized, non-blinded, non-control study.
Laser acupuncture (LA)	Hsieh 2016 (42)	PQAS, CINQ, OSNS scores, and touch-detection threshold and cold-trigger pain withdrawal latency all improved significantly after LA. LA significantly decreased the incidence and severity of neurotoxicity symptoms and impact the daily activities. (p<0.05) AEs: No serious adverse events	Class IV	Very low	Level U Insufficient	Small short term duration non-control cohort study.
Percutaneous auricular neurostimulation (PANS)	Sacco 2016 (51)	Pain score reduced significantly in PANS pre-post treatment (8.11 vs. 3.17, P < 0.001). no difference of number of treatments (mean 4.5) 59% patients with PANS showed marked improvements and 12.5% with minimal reductions of pain and numbness.	Class IV	Very low	Level U Insufficient	Small sample size, non-control retrospective study.
Acupuncture like transcutaneous nerve stimulation (ALTENS)	Wong 2016 (52)	ALTENS showed significant improvement in mTNS at 6 months compared to baseline (7.1 vs. 3.1, P < 0.001) Numbness score improved significant at 6 months. No changes in ESAS. AEs: no significant side effect reported. 3 patients reported a moderate aching discomfort at the stimulation sites; 1 patient developed mild skin rashes at one of the electrode sites.	Class IV	Very low	Level U Insufficient	Small sample size, non- real control, non RCT.
Sweet bee venom pharmacopuncture (SBVP)	Yoon 2012 (43)	Significant improvement was shown in WHO grade, VAS, Total HRQOL between baseline and after the last treatment session. Significant improvement was found in WHO grade, Total PNQ, PNQ-sensory, VAS, Total HRQOL and HRQOL-functional scores between baseline and 3 weeks after the final treatment. AEs: one patient had CTCAE grade 1, another had grade 2.	Class IV	Very low	Level U Insufficient	Small short term duration non-control study
Interferential therapy and long-wave diathermy at high power (ITH)	Lindblad 2016 (44)	No significant change in pain, discomfort, nerve symptoms, and balance disability between two groups No change in pain intensity in ITH at week 12 and 37 compared to baseline Significant improvement in discomfort, numbness and balance disability in ITH at week 12 and 37 compared to baseline.	Class II	Very low	Level U Insufficient	Small negative RCT with no sham control group. Downgrade to very low level of confidence in evidence

Table 6 (cont.). *Summary of level of evidence and recommendations*

Treatments	Study	Summary of Results	Level of Strength of Evidence	Level of Confidence in Evidence	Strength of the Recommendations	Comments
Low frequency magnetic field therapy	Geiger 2015 (45)	Sensory ataxia and sensory neuropathy had improvement after tx. (P < 0.05) No change in pain detect questionnaire, motor neuropathy.	Class IV	Very low	Level U Insufficient	One small sample size RCT phase III study. Downgrade to very low level of confidence in evidence.
	Rick 2017 (46)	NCV had significant improvement in MEF at 3 mons compared to PL (P = 0.015), particularly for sensory neurotoxicity. Significant improvement in CTCAE score in MEF at 3mons. (P = 0.04) No significant difference in neuropathic pain between MEF and PL.	Class II			
Scrambler therapy	Pachman 2015 (47)	Pain decreased by 53% P < 0.0001), numbness decreased by 37% (P = 0.0002) and tingling decreased by 44% (P < 0.0001) at day 10. Improvement in vibration perception and quality of life by global impression of change at week 10. AEs: no substantial adverse events.	Class IV	Very low	Level U Insufficient	Three small sample size, non RCT study.
	Coyne 2013 (48)	Pain scores reduced significantly from 6.6 to 4.5 at week 2, 4.6, 4.8 and 4.6 at 1, 2 and 3 mons. (P < 0.001) Significant improvement in BPI and BPI interference with normal life at week 2, 1, 2, and 3 mons Significant improvement in sensory and motor neuropathy by EORTC CIPN-20, particularly sensory improvement.	Class IV			
	Smith 2010 (49)	Significant improvement in 20% pain reduction, CIPN pain score, adjusted pain scores and daily reduction in pain scores at day 10, but no data for 1, 2 and 3 mons. CIPN pain score seems return baseline over 3 mons No significant change in change of use of pain drugs, quality of life, and other symptoms. AEs: No toxicity observed.	Class IV			

future CIPN treatment trials. Here we suggest that only CIPN patients who have an NRS pain score higher than 4/10 should be enrolled in trials in which pain intensity is primary outcome measure.

As far as the severity of the neuropathy evaluation, there are several commonly used tools including NCI-CTCAE, TNS/mTNS, WHO toxicity grading, NCS/EMG, the FACT/GOG-Ntx, EORTC-CIPN20 and PNQ. NCI-CTCAE is widely employed owing to its ease of use; it includes 2 items for use in clinical assessment of sensory and motor neuropathy, rated on a 0–4 grading scale. However, this tool is limited by its high rates of inter-observer disagreement and low sensitivity (8,28,53). TNS has 7 items covering 7 domains, sensory, motor, autonomic symptoms, pin sensitivity, vibration sensitivity, strength, and tendon reflexes, whereas modified TNS (mTNS) does not include autonomic symptom. mTNS was the most highly rated clinical assessment tool in a recent Delphi survey, and enables assessment of both small and large nerve fiber function (54). It is consistently reproducible and correlates with TNS, the gold standard of neuropathy assessment (33,53,55,56). The WHO toxicity grading scale, first published in 1979, developed a standardized approach to tumor treatment-related toxicity. The peripheral neuropathy section of this scale included measurements of paranesthesia, changes in deep tendon reflexes, and the extent of motor loss. However, it never became widely used for the assessment of CIPN (53). NCS/EMG is painful, time consuming, and only detects large myelinated fibers of involved peripheral nerves. Because some chemotherapy drugs, for instance bortezomib, affects small myelinated and unmyelinated fibers, these tests are not ideal for assessing CIPN or for monitoring therapeutic response. The FACT/GOG-Ntx and the EORTC-CIPN20 scales have high sensitivity, are directly relevant to CIPN-related functional deficits, and are well correlated with objective measures of neuropathy (57). FACT/GIG-Ntx contains 11 items divided into 5 sections: physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns. EORTC-CIPN20 contains 20 items assessing sensory (9 items), motor (8 items), and autonomic symptoms (3 items), on a 0-4 grading scale. Even though FACT/GOG-Ntx and EORTC-CIPN20 appear to be the most comprehensive CIPN assessment tools, they are time consuming and of limited usefulness for primary outcome assessment. However, PNQ consists of only 3 items, rated on a 0-4 grading scale assessing sensory, motor, and function loss. The PNQ is

convenient, and can be conducted without extensive equipment or training (54).

Despite broad and viable tools of outcome measures for CIPN, further study should focus on a tool with high reliability and reproducibility across examiners to assess CIPN. Here we consider that FACT/GOG-Ntx andEORTC-CIPN20 are more appropriate for secondary outcome measurements, as they are more comprehensive than some other tools, involving assessments of function and quality of life. From among the currently available assessment tools, we support Cavaletti and colleagues' recommendation to use the TNS/mTNS and measurements of pain intensity by NRS as the primary outcome measurements, as these tools allow the most effective descriptions of the type and severity of CIPN (53). In our review, 2 RCTs (25,33) with strong evidence adopted pain intensity and mTNS as primary outcome respectively.

Chemotherapeutic Agents

In order to better treat CIPN, a better understanding of the pathophysiological mechanisms of CIPN is needed. It is unclear why some agents that benefit diabetic peripheral neuropathic pain are not effective for treating CIPN (8,10,11). Several mechanisms are involved in diabetic peripheral neuropathy; for example, diabetes mellitus causes changes in ion channel expression in peripheral nerve fibers, which in turn leads to hyperexcitability. Therefore, in patients with diabetic neuropathic pain, dysregulation of voltage-gated calcium channels leads to an enhanced calcium influx in sensory neurons (58). The medications pregabalin and gabapentin are approved by the Food and Drug Administration for the first-line treatment of diabetic neuropathic pain because they selectively bind to presynaptic voltage-gated calcium channels in the brain and spinal cord, inhibiting of the release of excitatory neurotransmitters (59-61). However, those medications are not effective in CIPN, suggesting the mechanisms of CIPN differ from those underlying other forms of peripheral neuropathy.

The mechanisms of CIPN also seem to depend upon the type of chemotherapeutic medication used. CIPN can by caused by antimicrotubule agents (taxanes, including paclitaxel and docetaxel), platinum compounds (cisplatin, carboplatin, oxaliplatin), proteasome inhibitors (bortezomib), immunomodulatory agents (thalidomide and lenalidomide) and vinca alkaloids (vincristine, vinblastine, and vinorelbine). Bortezomib causes a painful length dependent small fiber axonal sensory neuropathy by inhibiting proteasomes, the primary intracellular protein degradation machinery in neurons (62). It also increases microtubule polymerization, and causes mitochondria to exhibit decreased axonal transport and function in sensory neurons (62). Thalidomide is thought to cause peripheral neuropathy via both its immunomodulation and antiangiogenic effects, resulting in partially irreversible damage to distal axons and dorsal root ganglion (DRG) neurons from capillary damage and secondary anoxemia in nerve fibers (63,64). The platinum-based chemotherapeutics drugs work by forming interstrand DNA adducts, leading to cell cycle arrest, but this antineoplastic mechanism may also cause CIPN through damaging DRG by forming adducts with nuclear and mitochondrial DNA (65,66). In addition, oxaliplatin's effect on voltage-gated sodium channel kinetics causes cold-induced dysesthesia in the hands and mouth (67). Taxane agents prevent microtubule depolymerization by binding to polymerized tubulin within microtubules in sensory neurons (68). Vinca alkaloids, which are used for the primary treatment of hematological malignancies, predominantly cause sensory neuropathy, with some degree of motor involvement. In the contrast to the taxane agents, vinca alkaloids promote microtubule depolymerization by binding to microtubules, disrupting mitotic spindles and causing cell cycle arrest (68). DRG sensory neurons, which are highly polarized, require proper microtubule function for axonal transport of mRNAs, proteins, mitochondria and other organelles. It helps to explain why these 2 drugs with opposite effects on microtubule stability both can cause CIPN (69,70). Although the mechanisms underlying CIPN are varied and unclear, most human and animal studies implicate axonal degeneration as a common process in CIPN pathology, which include defects in axon transport, altered mitochondrial function and altered calcium ion homeostasis (7).

A large negative RCT of topical KA reported no significant improvement in pain, numbness, and tingling scores at 3 and 6 weeks (35). However, the subgroup of patients who underwent taxane chemotherapy had significantly lower pain, numbness, and tingling scores than did patients in the non-taxane group at 6 weeks (35). These results suggest that topical KA may have benefits for patients whose CIPN is attributable to taxane agents. Given the varied mechanisms of chemotherapeutic agents, we consider that future study

designs should focus on a single type of chemotherapeutic agent causing CIPN in order to better determine the efficacy of CIPN treatment.

Timing of Treatment Entry

Table 4 outlines the timing of treatment entry for each study. Nineteen (54%) studies reported that CIPN treatment was initiated after completion of chemotherapy. Of those 19 studies, only 9 reported that the treatment started at least 3 months after completion of chemotherapy. In addition, 2 (6%) studies reported that the treatment started while patients were undergoing chemotherapy. Eight (23%) studies reported the timing of treatment occurred while patients had received and were receiving chemotherapy. Six (17%) studies were unclear on the timing of chemotherapy.

CIPN is fairly common within 1 month after cessation of chemotherapy, and its prevalence decreases over time. Approximately one-third of patients have chronic CIPN lasting 6 months or more after the end of chemotherapy (1). The lack of uniformity in the timing of treatment entry among studies makes the results less convinced and also makes between-study comparisons difficult. In 2 large positive RCTs, the timing of treatment entry was at least 1 or 3 months, respectively, after completion of chemotherapy (25,33). Another 2 large negative RCTs reported that CIPN treatment started while patients had received and were receiving chemotherapy (9,10). These data suggest that the timing of treatment entry should be a standardized element of study design. We consider that at least 3 months after completion of chemotherapy is an appropriate timing of the treatment entry point, as this period would allow adequate time for self-recovery of involved peripheral nerves after cessation of chemotherapy.

Limitations

This review, while comprehensive, had some limitations. It included only literature published in English and the included studies were relatively poor homogeneous, with variations in timing of treatment, primary outcomes and chemotherapeutic agents used.

Conclusions

These evidence-based clinical recommendations aimed to provide the best and most current evidence on the treatment of CIPN for physicians and patients. They have potential to improve the appropriateness and effectiveness of patient care by employing the best evidence available. In addition, these recommendations serve to identify knowledge, study design, and methodology gaps in the clinical literature on the treatment of CIPN. Future study should focus on using a standardized study design and outcome measures, large sample sizes and long-term follow-up for CIPN treatment trials.

Acknowledgments

Author Contributions: All authors had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Hou and Abdi designed the study protocol. Drs. Hou, Huh and Abdi managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. Drs. Huh and Kim provided revision for intellectual content and final approval of the manuscript.

Conflict of Interest: All authors have no conflicts of interest to report. All of the authors of the manuscript did not receive any remuneration.

Funding/support: The study was sponsored by grants from Helen Buchanan and Stanley Joseph Seeger Endowment at The University of Texas MD Anderson Cancer Center to Dr. Abdi. But the manuscript is separate and apart from the guidance of the sponsor.

Role of Sponsor: The financial sponsor of this work had no role in the design and conduct of the study or the collection, management, analysis, and interpretation of the data. The sponsor also did not have a role in the preparation or review of the manuscript or the decision to submit.

The authors also wish to thank Amy Ninetto, an editor in the Department of Scientific Publications, The University of Texas MD Anderson Cancer Center who edited the manuscript for non-intellectual content.

References

1. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, Colvin LA, Fallon M. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain* 2014; 155:2461-2470.
2. Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: A comprehensive survey. *Cancer Treat Rev* 2014; 40:872-882.
3. van den Heuvel SAS, van der Wal SEI, Smedes LA, Radema SA, van Alfen N, Vissers KCP. Intravenous lidocaine: Old-school drug, new purpose-reduction of intractable pain in patients with chemotherapy induced peripheral neuropathy. *Pain Res Manage* 2017; 2017:8053474.
4. Loprinzi CL, Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, Kamal A, Le-Lindqwister NA, Soori GS, Jaslowski AJ, Novotny PJ, Lachance DH. Natural history of paclitaxel-associated acute pain syndrome: Prospective cohort study NCCTG N08C1. *J Clin Oncol* 2011; 29:1472-1478.
5. Beijers A, Mols F, Dercksen W, Driessen C, Vreugdenhil G. Chemotherapy-induced peripheral neuropathy and impact on quality of life 6 months after treatment with chemotherapy. *Journal of Community and Supportive Oncology* 2014; 12:401-406.
6. Briani C, Argyriou AA, Izquierdo C, Velasco R, Campagnolo M, Alberti P, Frigeni B, Cacciavillani M, Bergamo F, Cortinovis D, Cazzaniga M, Bruna J, Cavaletti G, Kalofonos HP. Long-term course of oxaliplatin-induced polyneuropathy: A prospective 2-year follow-up study. *Journal of the Peripheral Nervous System* 2014; 19:299-306.
7. Fukuda Y, Li Y, Segal RA. A mechanistic understanding of axon degeneration in chemotherapy-induced peripheral neuropathy. *Front Neurosci* 2017; 11:481.
8. Kautio AL, Haanpaa M, Saarto T, Kalso E. Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms. *J Pain Symptom Manage* 2008; 35: 31-39.
9. Rao RD, Flynn PJ, Sloan JA, Wong GY, Novotny P, Johnson DB, Gross HM, Renno SI, Nashawaty M, Loprinzi CL. Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled trial, N01C3. *Cancer* 2008; 112:2802-2808.
10. Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, Warner DO, Novotny P, Kutteh LA, Wong GY. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer* 2007; 110:2110-2118.
11. Tsavaris N, Kopterides P, Kosmas C, Efthymiou A, Skopelitis H, Dimitrakopoulos A, Pagouni E, Pikazis D, Zis PV, Koufos C. Gabapentin monotherapy for the treatment of chemotherapy-induced neuropathic pain: A pilot study. *Pain Med* 2008; 9:1209-1216.
12. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL, American Society of Clinical O. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014; 32:1941-1967.
13. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. *Ann Neurol* 2017; 81:772-781.
14. Gewandter JS, Freeman R, Kitt RA, Cavaletti G, Gauthier LR, McDermott MP, Mohile NA, Mohlie SG, Smith AG, Tejani MA, Turk DC, Dworkin RH. Chemotherapy-induced peripheral neuropathy clinical trials: Review and recommendations. *Neurology* 2017; 89: 859-869.
15. Piccolo J, Kolesar JM. Prevention and treatment of chemotherapy-induced peripheral neuropathy. *American Journal of Health-System Pharmacy* 2014; 71:19-25.
16. Gronseth GW, LM.; Getchius, TS. Clinical practice guideline process manual. 2011 Ed. 2011.
17. Gronseth GW, LM.; Getchius, TS. Amendments to 2011 American Academy of Neurology Clinical Practice Guideline Process Manual. 2015.
18. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D. Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011; 76:1758-1765.
19. Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, Armstrong MJ, Gloss D, Potrebic S, Jankovic J, Karp BP, Naumann M, So YT, Yablon SA. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2016; 86:1818-1826.
20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *J Clin Epidemiol* 2009; 62:e1-e34.
21. Hou S, Kemp K, Grabois M. A systematic evaluation of burst spinal cord stimulation for chronic back and limb pain. *Neuromodulation* 2016; 19:398-405.
22. Schellinger PD, Bryan RN, Caplan LR, Detre JA, Edelman RR, Jaigobin C, Kidwell CS, Mohr JP, Sloan M, Sorensen AG, Warach S. Evidence-based guideline: The role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; 75:177-185.
23. Maestri A, De Pasquale Ceratti A, Cundari S, Zanna C, Cortesi E, Crino L. A pilot study on the effect of acetyl-L-carnitine in paclitaxel- and cisplatin-induced peripheral neuropathy. *Tumori* 2005; 91:135-138.
24. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain Symptom Manage* 2014; 47:166-173.
25. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL.

Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. *JAMA* 2013; 309:1359-1367.

26. Yang YH, Lin JK, Chen WS, Lin TC, Yang SH, Jiang JK, Chang SC, Lan YT, Lin CC, Yen CC, Tzeng CH, Wang WS, Chiang HL, Teng CJ, Teng HW. Duloxetine improves oxaliplatin-induced neuropathy in patients with colorectal cancer: An open-label pilot study. *Support Care Cancer* 2012; 20:1491-1497.
27. Hirayama Y, Ishitani K, Sato Y, Iyama S, Takada K, Murase K, Kuroda H, Nagamachi Y, Konuma Y, Fujimi A, Sagawa T, Ono K, Horiguchi H, Terui T, Koike K, Kusakabe T, Sato T, Takimoto R, Kobune M, Kato J. Effect of duloxetine in Japanese patients with chemotherapy-induced peripheral neuropathy: A pilot randomized trial. *Int J Clin Oncol* 2015; 20:866-871.
28. Otake A, Yoshino K, Ueda Y, Sawada K, Mabuchi S, Kimura T, Kobayashi E, Isobe A, Egawa-Takata T, Matsuzaki S, Fujita M, Kimura T. Usefulness of duloxetine for Paclitaxel-induced peripheral neuropathy treatment in gynecological cancer patients. *Anticancer Res* 2015; 35:359-363.
29. Hammack JE, Michalak JC, Loprinzi CL, Sloan JA, Novotny PJ, Soori GS, Tirona MT, Rowland KM, Jr., Stella PJ, Johnson JA. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. *Pain* 2002; 98:195-203.
30. Desideri I, Francolini G, Becherini C, Terziani F, Delli Paoli C, Olmetto E, Loi M, Perna M, Meattini I, Scotti V, Greto D, Bonomo P, Sulprizio S, Livi L. Use of an alpha lipoic, methylsulfonylmethane and bromelain dietary supplement (Opera(R)) for chemotherapy-induced peripheral neuropathy management, a prospective study. *Med Oncol* 2017; 34:46.
31. Cartoni C, Brunetti GA, Federico V, Efficace F, Grammatico S, Tendas A, Scaramucci L, Cupelli L, D'Elia GM, Truini A, Niscola P, Petrucci MT. Controlled-release oxycodone for the treatment of bortezomib-induced neuropathic pain in patients with multiple myeloma. *Support Care Cancer* 2012; 20:2621-2626.
32. Truini A, Biasiotta A, Di Stefano G, La Cesa S, Leone C, Cartoni C, Federico V, Petrucci MT, Cruccu G. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. *CNS Neurol Disord Drug Targets* 2011; 10:916-920.
33. Argenta PA, Ballman KV, Geller MA, Carson LF, Ghebre R, Mullany SA, Teoh DG, Winterhoff BJ, Rivard CL, Erickson BK. The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial. *Gynecol Oncol* 2017; 144:159-166.
34. Kus T, Aktas G, Alpak G, Kalender ME, Sevinc A, Kul S, Temizer M, Camci C. Efficacy of venlafaxine for the relief of taxane and oxaliplatin-induced acute neurotoxicity: A single-center retrospective case-control study. *Support Care Cancer* 2016; 24:2085-2091.
35. Gewandter JS, Mohile SG, Heckler CE, Ryan JL, Kirshner JJ, Flynn PJ, Hopkins JO, Morrow GR. A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy-induced peripheral neuropathy (CIPN): A University of Rochester CCOP study of 462 cancer survivors. *Support Care Cancer* 2014; 22:1807-1814.
36. Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD, 3rd, Kugler JW, Hoff KL, Reddy PS, Rowland KM, Jr., Riepl M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer* 2011; 19:833-841.
37. Fallon MT, Storey DJ, Krishan A, Weir CJ, Mitchell R, Fleetwood-Walker SM, Scott AC, Colvin LA. Cancer treatment-related neuropathic pain: proof of concept study with menthol--a TRPM8 agonist. *Support Care Cancer* 2015; 23:2769-2777.
38. Bao T, Goloubeva O, Pelser C, Porter N, Primrose J, Hester L, Sadowska M, Lapidus R, Medeiros M, Lao L, Dorsey SG, Badros AZ. A pilot study of acupuncture in treating bortezomib-induced peripheral neuropathy in patients with multiple myeloma. *Integr Cancer Ther* 2014; 13:396-404.
39. Schroeder S, Meyer-Hamme G, Epplee S. Acupuncture for chemotherapy-induced peripheral neuropathy (CIPN): A pilot study using neurography. *Acupunct Med* 2012; 30:4-7.
40. Donald GK, Tobin I, Stringer J. Evaluation of acupuncture in the management of chemotherapy-induced peripheral neuropathy. *Acupunct Med* 2011; 29:230-233.
41. Garcia MK, Cohen L, Guo Y, Zhou Y, You B, Chiang J, Orlowski RZ, Weber D, Shah J, Alexanian R, Thomas S, Romaguera J, Zhang L, Badillo M, Chen Y, Wei Q, Lee R, Delasalle K, Green V, Wang M. Electroacupuncture for thalidomide/bortezomib-induced peripheral neuropathy in multiple myeloma: A feasibility study. *J Hematol Oncol* 2014; 7: 41.
42. Hsieh YL, Chou LW, Hong SF, Chang FC, Tseng SW, Huang CC, Yang CH, Yang CC, Chiu WF. Laser acupuncture attenuates oxaliplatin-induced peripheral neuropathy in patients with gastrointestinal cancer: A pilot prospective cohort study. *Acupunct Med* 2016; 34:398-405.
43. Yoon J, Jeon JH, Lee YW, Cho CK, Kwon KR, Shin JE, Sagar S, Wong R, Yoo HS. Sweet bee venom pharmacopuncture for chemotherapy-induced peripheral neuropathy. *J Acupunct Meridian Stud* 2012; 5:156-165.
44. Lindblad K, Bergkvist L, Johansson AC. Evaluation of the treatment of chronic chemotherapy-induced peripheral neuropathy using long-wave diathermy and interferential currents: A randomized controlled trial. *Support Care Cancer* 2016; 24:2523-2531.
45. Geiger G, Mikus E, Dertinger H, Rick O. Low frequency magnetic field therapy in patients with cytostatic-induced polyneuropathy: A phase II pilot study. *Bioelectromagnetics* 2015; 36:251-254.
46. Rick O, von Hehn U, Mikus E, Dertinger H, Geiger G. Magnetic field therapy in patients with cytostatics-induced polyneuropathy: A prospective randomized placebo-controlled phase-III study. *Bioelectromagnetics* 2017; 38:85-94.
47. Pachman DR, Weisbrod BL, Seisler DK, Barton DL, Fee-Schroeder KC, Smith TJ, Lachance DH, Liu H, Shelerud RA, Cheville AL, Loprinzi CL. Pilot evaluation of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. *Support Care Cancer* 2015; 23:943-951.
48. Coyne PJ, Wan W, Dodson P, Swainey C, Smith TJ. A trial of Scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *J Pain Palliat Care Pharmacother* 2013; 27:359-364.
49. Smith TJ, Coyne PJ, Parker GL, Dodson P, Ramakrishnan V. Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare(R)) for chemotherapy-induced peripheral neuropathy. *J Pain Symptom Manage* 2010; 40:883-891.

50. Prinsloo S, Novy D, Driver L, Lyle R, Ramondetta L, Eng C, McQuade J, Lopez G, Cohen L. Randomized controlled trial of neurofeedback on chemotherapy-induced peripheral neuropathy: A pilot study. *Cancer* 2017; 123:1989-1997.
51. Sacco J, Baas W, Barnes MA, Luberto C, Talat R, Cotton S. The efficacy of percutaneous auricular neurostimulation for chemotherapy-induced peripheral neuropathy: A retrospective chart review. *Medical Acupuncture* 2016; 28:131-136.
52. Wong R, Major P, Sagar S. Phase 2 study of acupuncture-like transcutaneous nerve stimulation for chemotherapy-induced peripheral neuropathy. *Integr Cancer Ther* 2016; 15:153-164.
53. Cavaletti G, Frigeni B, Lanzani F, Mattavelli L, Susani E, Alberti P, Cortinovis D, Bidoli P. Chemotherapy-Induced peripheral neurotoxicity assessment: A critical revision of the currently available tools. *Eur J Cancer* 2010; 46:479-494.
54. McCrary JM, Goldstein D, Boyle F, Cox K, Grimison P, Kiernan MC, Krishnan AV, Lewis CR, Webber K, Baron-Hay S, Horvath L, Park SB. Optimal clinical assessment strategies for chemotherapy-induced peripheral neuropathy (CIPN): A systematic review and Delphi survey. *Support Care Cancer* 2017; 25:3485-3493.
55. Smith EM, Cohen JA, Pett MA, Beck SL. The reliability and validity of a modified total neuropathy score-reduced and neuropathic pain severity items when used to measure chemotherapy-induced peripheral neuropathy in patients receiving taxanes and platinums. *Cancer Nurs* 2010; 33:173-183.
56. Cornblath DR, Chaudhry V, Carter K, Lee D, Seysedadr M, Miernicki M, Joh T. Total neuropathy score: Validation and reliability study. *Neurology* 1999; 53:1660-1664.
57. Cavaletti G, Cornblath DR, Merkies IS, Postma TJ, Rossi E, Frigeni B, Alberti P, Bruna J, Velasco R, Argyriou AA, Kalofonos HP, Psimaras D, Ricard D, Pace A, Galie E, Briani C, Dalla Torre C, Faber CG, Lalisang RI, Boogerd W, Brandsma D, Koeppen S, Hense J, Storey D, Kerrigan S, Schenone A, Fabbri S, Valsecchi MG. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: From consensus to the first validity and reliability findings. *Ann Oncol* 2013; 24:454-462.
58. Hall KE, Liu J, Sima AA, Wiley JW. Impaired inhibitory G-protein function contributes to increased calcium currents in rats with diabetic neuropathy. *J Neurophysiol* 2001; 86:760-770.
59. Verma V, Singh N, Singh Jaggi A. Pregabalin in neuropathic pain: Evidences and possible mechanisms. *Curr Neuropharmacol* 2014; 12:44-56.
60. Zilliox L, Russell JW. Treatment of diabetic sensory polyneuropathy. *Curr Treat Options Neurol* 2011; 13:143-159.
61. Ziegler D, Schneider E, Boess FG, Berggren L, Birklein F. Impact of comorbidities on pharmacotherapy of painful diabetic neuropathy in clinical practice. *J Diabetes Complications* 2014; 28:698-704.
62. Chaudhry V, Cornblath DR, Polydefkis M, Ferguson A, Borrello I. Characteristics of bortezomib- and thalidomide-induced peripheral neuropathy. *J Peripher Nerv Syst* 2008; 13:275-282.
63. Kirchmair R, Tietz AB, Panagiotou E, Walter DH, Silver M, Yoon YS, Schratzberger P, Weber A, Kusano K, Weinberg DH, Ropper AH, Isner JM, Losordo DW. Therapeutic angiogenesis inhibits or rescues chemotherapy-induced peripheral neuropathy: Taxol- and thalidomide-induced injury of vasa nervorum is ameliorated by VEGF. *Mol Ther* 2007; 15:69-75.
64. Kerckhove N, Collin A, Conde S, Chaleteix C, Pezet D, Balayssac D. Long-term effects, pathophysiological mechanisms, and risk factors of chemotherapy-induced peripheral neuropathies: A comprehensive literature review. *Front Pharmacol* 2017; 8:86.
65. Johnstone TC, Park GY, Lippard SJ. Understanding and improving platinum anticancer drugs--phenanthriplatin. *Anticancer Res* 2014; 34:471-476.
66. Addington J, Freimer M. Chemotherapy-induced peripheral neuropathy: An update on the current understanding. *F1000Res* 2016:5.
67. Sittl R, Lampert A, Huth T, Schuy ET, Link AS, Fleckenstein J, Alzheimer C, Grafe P, Carr RW. Anticancer drug oxaliplatin induces acute cooling-aggravated neuropathy via sodium channel subtype Na(V)1.6-resurgent and persistent current. *Proc Natl Acad Sci U S A* 2012; 109:6704-6709.
68. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. *Nat Rev Cancer* 2004; 4:253-265.
69. Gornstein E, Schwarz TL. The paradox of paclitaxel neurotoxicity: Mechanisms and unanswered questions. *Neuropharmacology* 2014; 76 Pt A:175-183.
70. Geisler S, Doan RA, Strickland A, Huang X, Milbrandt J, DiAntonio A. Prevention of vincristine-induced peripheral neuropathy by genetic deletion of SARM1 in mice. *Brain* 2016; 139:3092-3108.