

A systematic review of acupuncture for chemotherapy-induced peripheral neuropathy

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ABSTRACT

Objectives In cancer patients, chemotherapy-induced peripheral neuropathy (CIPN) is a common complication, characterized by pain, loss of sensation, and numbness. Medical treatment for peripheral neuropathies has been shown to be ineffective for CIPN. Acupuncture has been shown to be safe and effective in treating cancer-related symptoms and other peripheral neuropathies. For the present review, we aimed to evaluate the efficacy of acupuncture for the treatment of CIPN.

Design Comprehensive searches for relevant studies were conducted in Ovid EMBASE, the Web of Science, Ovid MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (EBSCO Information Services, Ipswich, MA, U.S.A.), and the ClinicalTrials.gov Web site. References from previous systematic reviews were also searched. Additional trials were found in the reference lists of relevant papers and in searches of Google Scholar and acupuncture-specific Web sites. Included studies were randomized controlled trials (RCTs) of any type of acupuncture used to treat patients with CIPN.

Results Three clinical trials (203 participants) were included. Two studies found acupuncture to be effective in alleviating CIPN pain and improving quality of life. One study found no benefit in improving neuropathic pain, symptoms, or quality of life. Study quality was variable and included a moderate overall risk of bias.

Conclusions The evidence is insufficient to recommend acupuncture for the treatment or prevention of CIPN. Further research is needed to evaluate the effects of acupuncture in the treatment of CIPN. Given that acupuncture is considered safe and might provide relief for patients, it can be considered at the clinician's discretion.

Key Words Acupuncture, systematic reviews, chemotherapy-induced peripheral neuropathy, CIPN, integrative oncology

Curr Oncol. 2019 April;26(2):e147-e154

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INTRODUCTION

Most anticancer treatments have significant side effects. It is well understood that chemotherapy drugs are neurotoxic and can damage peripheral nerves, ultimately resulting in chemotherapy-induced peripheral neuropathy (CIPN)¹. Patients with CIPN can experience any or all of neuropathic pain (allodynia), loss of sensation, and loss of motor function in a stocking-glove distribution.

Unfortunately, CIPN is common, with 68.1% of patients developing it within the first month of chemotherapy². Furthermore, CIPN can persist for years and significantly affects quality of life for cancer patients. A recent study of 362 patients showed a highly significant ($p < 0.0005$) inverse correlation between CIPN symptoms and quality of life³. Associations of CIPN with increased depressive symptoms

and reduced sleep quality have been observed^{4,5}. More importantly, however, CIPN might limit the effectiveness of anticancer treatments because a common management strategy is to reduce the dose of chemotherapy⁶.

Although effective symptomatic treatments for other peripheral neuropathies not induced by chemotherapy are available (for example, gabapentin, tricyclic antidepressants), the evidence for their use in CIPN is inconclusive⁷. Duloxetine is the only symptomatic treatment for CIPN backed by a randomized controlled trial (RCT), and even then, the therapeutic effect is modest⁸. Treatments for CIPN prevention backed by RCTs are limited^{8,9}. Some inconclusive data suggest that lafutidine might prevent the development of severe CIPN (but without decreasing its occurrence)¹⁰. Additionally, a recent RCT demonstrated that a 6-week exercise program is effective in preventing CIPN¹¹. Given

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E-mail: kevin94li@alumni.ubc.ca ■ DOI: <https://doi.org/10.3747/co.26.4261>
Supplemental material available at <http://www.current-oncology.com>

the morbidity of CIPN and limited conventional means for management, it is imperative to look for better alternatives.

Acupuncture therapy, associated with Traditional Chinese Medicine, has a long history in treating pain. Acupuncture is well-accepted and safe, and adverse effects are quite rare¹². Moreover, acupuncture is currently practiced in oncology settings¹³ and has been shown to be effective in treating other cancer-related symptoms such as pain^{14,15}; nausea and vomiting¹⁶; xerostomia induced by radiation therapy^{17,18}; fatigue¹⁹; and anxiety, depression, and insomnia²⁰. Acupuncture has also demonstrated benefits in treating other peripheral neuropathies such as diabetic neuropathy, Bell palsy, and carpal tunnel²¹.

Franconi *et al.*²² conducted the most recent systematic review of the use of acupuncture in CIPN. They found seven records, of which three were RCTs, and only two assessed patients with CIPN. Both studies found acupuncture to be effective for CIPN, but because the full texts of the studies were in Chinese, it is difficult to evaluate the quality of the data. Given that additional clinical trials have been conducted since that review, we felt that it was important to reassess the literature. Here, we evaluate the efficacy of acupuncture compared with controls (placebo, sham acupuncture) in treating and preventing CIPN. As a secondary objective, we discuss the current understanding of acupuncture mechanisms to provide some insight into how this treatment might play a role in managing CIPN. A key difference between our study and the previous systematic review is that we include only high-quality RCTs. The previous review also failed to critically appraise study quality with respect to risk of bias and methodology, which we have done here, using validated tools.

METHODS

Database Search

In May 2017, we performed searches in the following databases: Ovid EMBASE, Web of Science, Ovid MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (EBSCO Information Services, Ipswich, MA, U.S.A.), the ClinicalTrials.gov Web site, and the AcuTrials database (Oregon College of Oriental Medicine, Portland, OR, U.S.A.). To ensure high search sensitivity, grey literature searches were performed in high-yield databases and acupuncture Web sites identified by Cogo *et al.*²³ (Acudoc2, Index to Chiropractic Literature, PsycInfo). The systematic searches were designed with input from a medical librarian (DG) and adjusted for each database to account for indexing and keyword search functionality (supplemental Appendix 1). Additional studies from previous systematic reviews^{21,22,24} and Google Scholar searches were also identified.

Study Selection and Data Extraction

Using Mendeley (Elsevier, Amsterdam, Netherlands), records retrieved from our searches were aggregated, and duplicates were removed (Figure 1). Abstracts were screened for relevance, and the rationale behind screening choices were recorded in Rayyan²⁵. Articles were considered relevant when they met the eligibility criteria for the intervention (acupuncture), population (patients with CIPN), control (standard treatment, placebo, sham

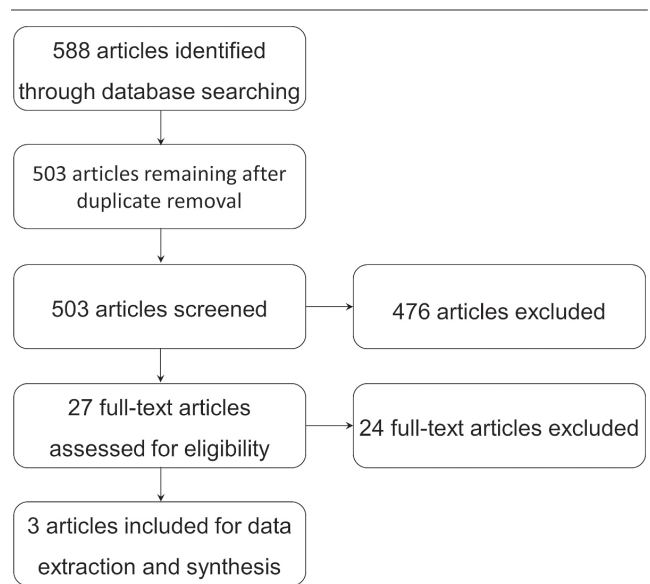


FIGURE 1 PRISMA flow chart for the study selection process.

acupuncture, or no acupuncture), and outcomes (CIPN symptoms, CIPN prevention). Within the pool of relevant records, the full text was evaluated for eligibility based on an RCT study design (non-RCTs were excluded). The study selection process was completed by one researcher (KL), and the results were reviewed by the research supervisor (DS). Data extraction was completed using a data extraction tool adapted from the data collection form developed by the Cochrane Effective Practice and Organization of Care Group²⁶, and the articles were critically appraised using the Cochrane Risk of Bias tool²⁷ and the STRICTA checklist²⁸. Data extraction and risk-of-bias assessments were completed by one researcher (KL).

Inclusion Criteria

Included studies were human RCTs, in which acupuncture was an independently applied intervention and CIPN was one of the *a priori* primary or secondary outcomes evaluated. Participants in those studies must have had chemotherapy treatment and symptoms of CIPN. Included studies could use any form of acupuncture treatment, including acupuncture, electro-acupuncture, or acupressure as an adjunctive or main intervention. The intervention must have been compared with an appropriate control (standard treatment, placebo, sham acupuncture, or no acupuncture). The studies must have assessed one or more of the following outcomes (adapted from Franconi *et al.*²²):

- Pain, as defined by any grading scale
- Numbness, tingling, cold sensitivity, or any other signs of peripheral neuropathy
- Subjective patient reports
- Surrogate markers that might explain the mechanisms by which acupuncture treats CIPN
- Activities of daily living
- Quality of life measures
- Safety
- Changes in chemotherapy dosing

Exclusion Criteria

Studies other than RCTs (preclinical studies, observational studies, qualitative studies, case reports, and nonrandomized or non-controlled studies) were excluded. Studies assessing patients who were experiencing types of neuropathy other than CIPN (diabetic neuropathy, HIV), and non-English-language studies were also excluded.

Review Protocol

Before the data from the search were extracted, the protocol for this review was registered at the PROSPERO international prospective register of systematic reviews (registration number: CRD4201706). It can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017067745.

RESULTS

Search Results

The searches identified a total of 588 records (Figure 1). After duplicates were removed, the remaining 503 records were screened for relevance. During the screening process, 476 records were excluded because they were not relevant to CIPN or did not use a variation of acupuncture as an intervention. The remaining twenty-seven records were assessed for eligibility based on their full text. After full-text screening, twenty-four records were excluded based on inadequate study design. Within the twenty-four excluded studies, two assessed an inappropriate outcome (prevention of CIPN), one was a conference abstract of an included journal article, five did not assess CIPN, one was written in Chinese, one used an inadequate placebo, seven were non-RCTs, three were protocols, and four used acupuncture-like therapies not outlined in our inclusion criteria (supplemental Appendix 2). Three records were included for qualitative synthesis.

Study Characteristics

The three included studies assessed acupuncture's efficacy in treating CIPN pain and CIPN-associated quality of life (Table 1). The sample sizes in the studies varied from 40 to 104, with the total sample size being 203. The studies assessed patients with breast cancer and multiple myeloma experiencing CIPN caused by chemotherapeutic agents including taxanes, platinum derivatives, or vinca alkaloids. Each trial used acupuncture or electro-acupuncture as the intervention, with a primary outcome associated with CIPN. The controls used in the studies varied and included oral and injection methylcobalamin, delayed low-dose acupuncture treatment, hydroelectric baths, vitamin B complex capsules, and placebo (lactose capsules). The duration of the intervention varied in the range of 3–12 weeks, and the frequency of treatment varied from weekly to 3 times per week. In the studies overall, 1 adverse event (swelling, discomfort, and bruising) was reported.

Risk of Bias

The included studies generally had a low or unclear risk of bias (Figure 2). Random sequence allocation was adequately used in two of the studies^{29,30}, but was unclear in the study by Lu and colleagues³¹. Only one trial adequately

concealed the participant's assignment from the investigators³⁰; it was unclear whether such concealment was done in the other two studies. Participants or personnel, or both, were not blinded in two studies^{29,30}, but blinding status was not made clear in the study by Lu and colleagues³¹. Blinding of investigators involved in outcome assessment was not clear in any study^{29–31}. Incomplete outcomes data were sufficiently explained and were deemed to carry a low risk of bias for all the studies except for that by Lu and colleagues. Outcomes were also not selectively reported in one study²⁹, but selectivity of reporting was unclear in the other two^{30,31}. Lastly, all studies (aside from the study by Lu and colleagues³¹) were considered to be free of other biases.

It should be noted that, because the study by Lu and colleagues³¹ was a conference abstract, many of the details required for risk of bias assessment were not available. Given that our sample size was inherently limited, we felt it necessary to include that study despite the unclear risk of bias. The author was contacted to clarify relevant details, but no response was received. The study was therefore deemed to have an unclear risk of bias across all domains.

STRICTA Checklist

Table II summarizes the appraisal of study quality based on the STRICTA checklist. None of the studies satisfied all of the STRICTA criteria, but two studies met all but 4 of the checklist items^{29,30}. Excluding the abstract by Lu and colleagues³¹, the style of acupuncture and the extent of treatment variance was described by all studies. No study adequately provided a rationale for the treatment provided. Two studies^{29,30} reported most of the details of their acupuncture technique, but one study did not report any details³¹. No studies reported the number of needle insertions per session. The treatment regimen (number of sessions, frequency and duration of sessions) was reported clearly in all studies. Details of other interventions administered to the acupuncture group were explained in two studies^{29,30}, but were not mentioned in one study³¹. The setting and context of treatment were not adequately reported in all studies. Details and qualifications of the acupuncturists and the rationale for controls were described in two studies^{29,30}, but not in the study by Lu and colleagues³¹. All studies provided a precise description of the control group^{29–31}.

Results of Individual Studies

Two studies showed that acupuncture was effective for CIPN pain and CIPN-associated quality of life^{30,31}, and one study showed that it was ineffective for CIPN pain, neuropathy score, and quality of life²⁹.

DISCUSSION

Summary of Results

Of the three studies evaluated, two showed positive effects of acupuncture^{30,31}. Han *et al.* and Lu *et al.* both showed that acupuncture was more effective than its control for pain management and improved functional quality of life. The study by Rostock *et al.*²⁹ failed to show acupuncture's efficacy in improving neuropathic pain, symptoms, and quality of life. Given that the studies are inconsistent, it is inconclusive whether acupuncture is efficacious for CIPN.

TABLE 1 Summary of methods and results of included studies

Reference	Sample size	Sex	Cancer type and stage	Chemotherapy	Acupuncture		Frequency and duration		
					Intervention	Control	Intervention	Control	
Rostock <i>et al.</i> , 2013 ²⁹	59	Men and women	Not specified	Taxanes, platinum derivatives, or vinca alkaloids	Electroacupuncture	Three groups: ■ Hydroelectric baths ■ Vitamin B complex capsules ■ Placebo (lactose) capsules	2–3 Times weekly for 3 weeks (total of 8 sessions)	Control	
<p><i>Outcomes assessed:</i></p> <ul style="list-style-type: none"> ■ Primary: patient-reported CIPN severity (score on the numerical rating scale for neuropathic symptoms) ■ Secondary: neuropathy score, electroneurography, <i>Common Toxicity Criteria</i>^a, QLQ-C30^b <p><i>Results:</i> Acupuncture no more effective than control treatments: no significant difference in outcome improvement (primary or secondary) between acupuncture group and control groups.</p>									
Han <i>et al.</i> , 2017 ³⁰	104	Men and women	Multiple myeloma, all stages	All chemotherapy treatments	Acupuncture and methylcobalamin	Methylcobalamin	Approximately 3 times weekly for 12 weeks	Every other day or daily for 12 weeks	
<p><i>Outcomes assessed:</i> Degree of CIPN using VAS pain scores, score on the FACT/GOG-Ntx^c, and nerve conduction velocities</p> <p><i>Results:</i> Compared with methylcobalamin, acupuncture was effective for CIPN: significant decrease in VAS pain scores ($p<0.01$), and FACT/GOG-Ntx scores ($p<0.05$); no significant difference in nerve conduction velocities between acupuncture and controls ($p>0.05$)</p>									
Lu <i>et al.</i> , 2017 ³¹	40	Women	Breast cancer, stages I–III	Not specified	Acupuncture	Low-dose acupuncture, delayed 8 weeks after intervention	2–3 Times weekly for 8 weeks (total of 18 sessions)	1–2 Times weekly for 8 weeks (total of 9 sessions)	
<p><i>Outcomes assessed:</i> Degree of CIPN using the PNQ, FACT-Ntx^c, QLQ-CIPN20^b</p> <p><i>Results:</i> Acupuncture better than low-dose acupuncture for CIPN: significant improvement compared with control on the PNQ ($p=0.02$), the FACT-Ntx ($p=0.002$), and the QLQ-CIPN20 ($p=0.006$)</p>									

^a U.S. National Cancer Institute, Bethesda, MD.
^b European Organisation for Research and Treatment of Cancer, Brussels, Belgium.
^c FACIT.org, Elmhurst, IL, U.S.A.
 CIPN = chemotherapy-induced peripheral neuropathy; QLQ-C30 = 30-question core Quality of Life Questionnaire; VAS = visual analogue scale; FACT/GOG-Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group 12-item neurotoxicity scale; PNQ = Patient Neurotoxicity Questionnaire; FACT-Ntx = Functional Assessment of Cancer Therapy–Neurotoxicity; QLQ-CIPN20 = Quality of Life Questionnaire, 20-item chemotherapy-induced peripheral neuropathy scale.

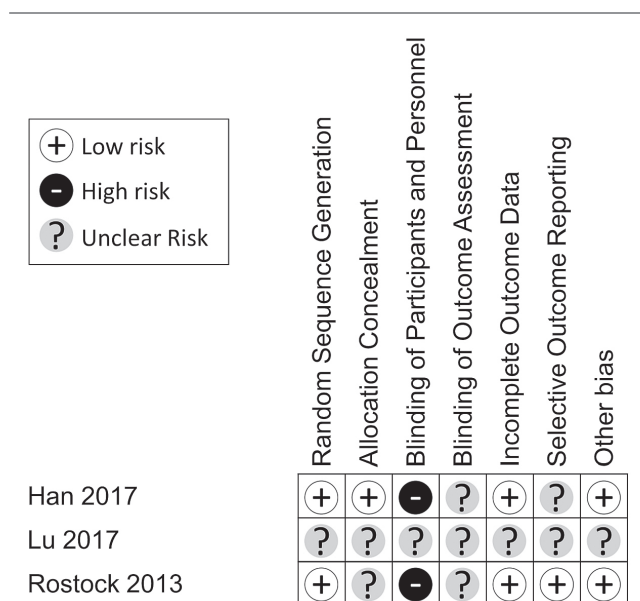


FIGURE 2 Risk-of-bias assessment for the included studies. Studies were evaluated using the Cochrane Risk of Bias tool and were classified under each category as low, high, or unclear risk of bias.

Within the three studies, only 1 mild adverse event was reported. That observation is consistent with previous studies that have shown acupuncture to be a safe therapy, with few and minor associated adverse effects¹².

Of special note is a study by Greenlee *et al.*³² that assessed acupuncture in preventing CIPN and that failed to show efficacy for acupuncture compared with placebo (sham acupuncture). We include that study in our discussion because it pertains to a similar topic and might be useful for discerning patterns.

Meta-analysis

Because of the heterogeneity of the study methods, a meta-analysis was not conducted. Studies varied in acupuncture protocol, acupuncture type, participant population, control therapy, and outcome assessment.

Concerns About the Studies

A few important points should be mentioned for the studies showing lack of benefit. The study by Rostock *et al.*²⁹ was terminated prematurely because, at the interim analysis stage, electro-acupuncture failed to show efficacy compared with placebo (determined using a predefined statistical threshold). The absolute improvement in pain was also less in the electro-acupuncture group than in the control group, but the difference was not statistically significant. Moreover, the study by Greenlee *et al.*³² showed that acupuncture might delay recovery from CIPN symptoms after chemotherapy is discontinued. Although inconclusive, those results are of concern from a caregiver's perspective.

Patterns Within Studies

The trials using acupuncture showed a positive effect^{30,31}, whereas the trials testing electro-acupuncture showed a lack of benefit^{29,32}. It is possible that only standard

acupuncture, rather than electro-acupuncture, is effective for CIPN. Furthermore, the only study involving multiple myeloma patients³⁰ showed benefit for acupuncture, but in the two studies involving breast cancer patients^{31,32}, results were mixed. One study showed benefit³¹; the other showed lack of benefit³². Perhaps the effectiveness of acupuncture varies with the cancer population.

Because the mechanism of CIPN differs depending on the chemotherapeutic agents administered¹, it might be hypothesized that efficacy could vary depending on the chemotherapeutic agent used. However, the results of our study do not support that hypothesis. Of the two trials^{31,32} assessing patients with taxane-induced CIPN, only one³¹ showed benefit. Another trial²⁹ assessed CIPN induced by several chemotherapeutic agents, and the study by Han³⁰ did not specify the agent used. Thus, the literature does not suggest that the chemotherapeutic agent or agents affect the efficacy of acupuncture.

Mechanisms of Acupuncture in CIPN

It is generally accepted that chemotherapeutic agents cause CIPN through oxidative stress within neurons, axonal degeneration, neuro-inflammation, and unbalanced calcium homeostasis¹. Neuro-inflammation might be a mechanistic target of acupuncture. Chemotherapeutic agents cause neuro-inflammation by activating immune cells to release inflammatory cytokines¹. Because acupuncture has been shown to have an anti-inflammatory effect by modulating cytokines and increasing calcitonin gene-related peptide³³, it is plausible that acupuncture might improve CIPN symptoms by reducing neuro-inflammation.

Other mechanisms of acupuncture have also been hypothesized. Acupuncture might reduce pain by inhibition of cyclooxygenase-2³⁴, release of endogenous opioids^{35,36}, and modulation of nociception^{35,37}. Acupuncture for CIPN might act through a combination of those mechanisms. Given that few studies have assessed the mechanism of acupuncture in CIPN, the literature does not provide clear guidance in this area.

Study Strengths and Limitations

A strength of our review is that we assessed only RCTs known to have the lowest risk of bias. Those trials all compared acupuncture with a control, used adequate random sequence generation, and accounted for incomplete outcomes data. Also, one of the studies had previously published protocols that matched their report. The risk of reporting bias in that study was low³⁰. To minimize incomplete retrieval of studies, we established our search protocol with the help of a medical librarian, and we conducted exhaustive searches in seven databases and Web sites.

The limitations of our study are that the total sample size was small ($n = 203$) and that the risk of bias in most categories was considered to be unclear. The small sample size was a result of too few RCTs on this topic being available. There were, however, many non-controlled and nonrandomized trials that were not reviewed. In addition, our study might also have inherent reporting or selection biases, given that the entire review was conducted by one individual (KL). That bias was minimized by having the study results reviewed by the project supervisor (DS).

TABLE II STRICTA checklist assessment of reporting quality

Item	STRICTA criterion	Reference		
		Rostock <i>et al.</i> , 2013 ²⁹	Han <i>et al.</i> , 2017 ³⁰	Lu <i>et al.</i> , 2017 ³¹
1. Acupuncture rationale	a) Style of acupuncture (for example, Traditional Chinese Medicine, Japanese, Korean, Western medical, etc.) b) Reasoning for treatment provided, literature source or consensus methods (or both), with references where appropriate c) Extent to which treatment was varied	Yes No Yes	Yes No Yes	No No No
2. Details of needling	a) Number of needle insertions per subject per session (mean and range where relevant) b) Names (or location if no standard name) of points used (unilateral or bilateral) c) Depth of insertion, based on a specified unit of measurement d) Response sought (for example, <i>de qi</i> sensation or muscle twitch response) e) Needle stimulation (for example, manual, electrical) f) Needle retention time	No Yes No Yes Yes Yes	No Yes Yes Yes No Yes	No No No No No No
3. Treatment regimen	a) Number of treatment sessions b) Frequency and duration of treatment sessions	Yes Yes	Yes Yes	Yes Yes
4. Other components of treatment	a) Details of other interventions administered to the acupuncture group (for example, moxibustion, cupping, herbs, exercises) b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	Yes No	Yes No	No No
5. Practitioner background	Description of participating acupuncturists (qualification or professional affiliation, other relevant experience)	Yes	Yes	No
6. Control or comparator interventions	a) Rationale for the control or comparator in the context of the research question, with sources that justify the choice b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, complete items 1 to 3 for the comparator as well as for the intervention.	Yes Yes	Yes Yes	No Yes

STRICTA = Standards for Reporting Interventions in Controlled Trials of Acupuncture.

Challenges of Acupuncture Studies

It is fundamentally difficult to objectively assess acupuncture, because there are many variations of acupuncture, and treatment methods are practitioner-dependent. That difficulty is evident from our review: the included studies show great variation with respect to acupuncture protocol and placebo therapy.

Placebo therapy varies because there is no generally agreed-upon placebo control. Placebos vary from acupressure, to sham acupuncture, to methylcobalamin injections, to placebo pills. Even within sham acupuncture, many variations are seen (low-dose therapy, needling non-acupoint areas, or using non-penetrating Streitberger needles, for instance). Some of those placebos also prevent adequate participant blinding (that is, patients can clearly identify whether they are receiving a pill or acupuncture). Moreover, unless a machine is used to perform the acupuncture protocol, it is extremely difficult to blind the personnel administering acupuncture.

Dimitrova *et al.*²¹ recently published a standardized protocol that could be used as a guideline for future studies in peripheral neuropathy. Further studies establishing “gold standard” acupuncture protocols, placebos, and outcomes for peripheral neuropathy will allow for a more reliable, objective assessment of acupuncture. We recognize that achieving a good placebo control for acupuncture is challenging. However, it is our opinion that finding that placebo is still the approach that could establish a true sense of the specific effects of acupuncture in this setting and for other clinical conditions

Comparison to Duloxetine in Future Trials

None of the included studies compared acupuncture with duloxetine, a drug previously established to be effective for CIPN. Although duloxetine is not the “gold standard” for CIPN, it is currently the most effective known treatment. Thus, we would recommend that future studies use this medication as a comparator in addition to placebo or sham acupuncture controls.

CONCLUSIONS

Although two of three included studies showed efficacy, it is difficult to offer a strong recommendation for the use of acupuncture in CIPN because of limited data and sample sizes. It is possible that only acupuncture, and not electro-acupuncture, is effective for CIPN. Both trials using acupuncture showed a positive effect^{30,31}, whereas the trials testing electro-acupuncture showed a lack of benefit^{29,32}. Two studies in our review also suggested potential harms of acupuncture for CIPN, although those observations were not statistically significant^{29,32}. However, acupuncture has previously been proved to be safe, and it is already used in oncology settings^{12,13}. Acupuncture could be chosen as an inexpensive, safe alternative treatment, but clinicians should use due diligence and vigilant monitoring when recommending acupuncture therapy. Given that the quality and quantity of the literature concerning this topic are limited, a potentially beneficial effect might exist, but future rigorous RCTs with appropriate controls should be conducted.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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