Review Article

Evaluating Acupuncture for the Treatment of Chemotherapy-induced Peripheral Neuropathy: An Integrative Review

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Abstract

The purpose of this integrative review of the literature is to synthesize the current evidence and identify gaps in knowledge regarding the effectiveness of acupuncture to treat chemotherapy-induced peripheral neuropathy (CIPN). PubMed, CINAHL, Web of Science, and Cochrane Review databases were searched using inclusion criteria: keywords acupuncture, cancer, and peripheral neuropathy, published in English, between 2009 and 2019. Sixteen articles met the inclusion criteria. The literature indicates that acupuncture is generally well tolerated by patients with cancer, and a majority of patients with CIPN reported decreased pain and increased quality of life after receiving acupuncture treatment. A comprehensive understanding of the ability of acupuncture to treat CIPN is limited by variability of acupuncture techniques and inconsistency in measures of evaluation.

Keywords

acupuncture, electro-acupuncture, chemotherapy-induced peripheral neuropathy, integrative oncology, cancer, integrative review

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side-effect of neurotoxic chemotherapy, experienced by an estimated 30%–40% of patients with cancer (Staff et al., 2017). Common symptoms of CIPN include burning, pain, tingling, numbness, and altered touch sensation (Hershman et al., 2014; Starbova & Vetter, 2017; Zajaczkowska et al., 2019). Other symptoms may include difficulty with balance and walking, and overall decreased quality of life (Bao et al., 2016; Hammond et al., 2019). The severity of symptoms associated with CIPN is considered to be higher than neuropathy from other causes, such as diabetes, as CIPN is commonly associated with higher pain levels (Zajączkowska et al., 2019). Additionally, CIPN symptoms often become progressively worse with higher single doses of chemotherapy and cumulative effect of multiple treatments (Hershman et al., 2014; Starbova & Vetter, 2017; Zajączkowska et al., 2019). Depending on the type of chemotherapy received, onset of CIPN may begin as soon as during treatment, or up to weeks or months following completion of chemotherapy (Starbova & Vetter, 2017; Zajączkowska et al., 2019). The effects of CIPN may have a profound effect on quality of life for patients with cancer and survivors, lasting up to several years into survivorship (Bao et al., 2016; Song et al., 2017; Tofthagen et al., 2020; Zajączkowska et al., 2019). Higher levels of CIPN among cancer survivors are associated with increased levels of anxiety, depression, insomnia, obesity, and incidence of falls (Bao et al., 2016; Kolb et al., 2016; Song et al., 2017; Starbova & Vetter, 2017).

Integrative oncology has been defined as an area of cancer care that involves the combination of practices from different traditions, including mind-body therapies and natural products, alongside conventional treatments to promote quality of life (Witt et al., 2017). The use of acupuncture is increasing in integrative oncology settings (Li et al., 2019; Z. Lu et al., 2017). Acupuncture is a technique that involves insertion of sterile needles into the skin at specific locations based on theories of Traditional Chinese Medicine (TCM) that are over 2,000 years old (Kaptchuk, 2002). The goal of TCM acupuncture therapy is to reduce or alleviate symptoms based upon a holistic perspective in which stimulation of specific points promotes healing through resolution of imbalances in the body (Kaptchuk, 2002). Although not completely understood, physiological mechanisms of acupuncture

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may include stimulation of neurotransmitters and modulation of peripheral and central nervous system pathways (Wu et al., 2016; Zhou & Benharash, 2014). A survey of acupuncturists working in integrative oncology indicated that CIPN is the most common condition treated, comprising about a third of patients (Lu et al., 2017).

Despite the increasing use of acupuncture for CIPN in integrative oncology, prior reviews have drawn divergent conclusions to support its use. The earliest systematic review, Franconi et al. (2013), concluded that there is limited evidence to support use of acupuncture for CIPN, and that more, higher quality research is needed as many studies have several limitations including small sample sizes and lack of controls. A recent meta-analysis by Chien et al. (2019), which included six RCT's (Greenlee et al., 2016; Han et al., 2017; Lu et al., 2019; Molassiotis, Suen, et al., 2019; Rostock et al., 2013; Zhang et al., 2017), found that acupuncture decreased subjective symptoms of CIPN in four studies (Han et al., 2017; Lu et al., 2019; Molassiotis, Suen, et al., 2019; Zhang et al., 2017), but that there was no correlation in objective measures including nerve conduction velocity (Han et al., 2017; Molassiotis, Suen, et al., 2019) and immune cytokines (Zhang et al., 2017). Two systematic reviews on the use of acupuncture for treatment of CIPN were published in 2019. Baviera et al. (2019) determined that acupuncture is of benefit for symptoms of CIPN, while Li et al. (2019) found insufficient evidence for recommendation in clinical practice. These conclusions were drawn based upon evaluation of different sets of primary studies. Li et al. (2019) selected randomized controlled trials (RCTs) involving any type of acupuncture, while Baviera et al. (2019) excluded studies if the acupuncture protocol involved electro-acupuncture (EA) or auricular acupuncture.

To address this gap, an integrative review of the literature was performed to evaluate the use and efficacy of acupuncture in the management of CIPN. Integrative reviews of the literature incorporate a wider range of articles and study designs in order to fully assess the state of the science, with aims including enhanced understanding of concepts and methodological issues (Hopia et al., 2016; Whittemore & Knafl, 2005). Acupuncture research has historically focused on experimental studies, which have faced several challenges including the selection of appropriate comparison groups (Zhuang et al., 2013). This integrative review of the literature fills an important gap in knowledge by providing a more complete and comprehensive view of what is currently known about acupuncture for the management of CIPN.

Purpose

The purpose of this integrative review of the literature is to synthesize the current evidence and identify gaps in knowledge regarding the effectiveness of acupuncture to treat CIPN through a comprehensive evaluation of the current literature. Additional recommendations for future research involving acupuncture for CIPN are provided.

Methods

Search Strategy

For the purposes of this integrative review, acupuncture is defined as the insertion of a needle into an acupuncture point located on the body, inclusive of auricular acupuncture and EA in order to include multiple, common acupuncture styles that involve needle insertion. This distinction is important and impacted the search results. For example, articles that focused on techniques that involve stimulating the location of acupuncture points by methods other than needle insertion—such as non-inserted needles, lasers, press balls, acupressure, or reflexology—were excluded. Additionally, neuropathy was limited to CIPN. The search included terms specific to oncology in order to limit results related to neuropathy from other etiologies, such as diabetes or HIV. Additional search criteria included studies published in English. The final search included articles published within the past ten years (2009–2019) in order to capture clinically relevant data that would reflect current practice in integrative oncology settings. The time period of the search was expanded from five to ten years after a prior search for articles within the past five years produced only six articles of direct relevance to the research question.

The literature was reviewed using the electronic databases PubMed, CINAHL, Web of Science, and Cochrane Review. These databases include Chinese-language journals that have been translated into English. Therefore, Chinese-language databases were not included. The search strategy was completed using the keywords acupuncture, cancer, and peripheral neuropathy. MeSH terms included acupuncture therapy, neoplasm, carcinoma, and peripheral nervous system disorders. The search strategy, including selection of terms and relevant databases, was performed in consultation with the health sciences librarian.

Data Management

A total of 220 articles were identified in the initial search (Figure 1). After duplicates were removed, 105 articles remained. Articles were further excluded if titles indicated that (a) the study was not directly related to the research question, for example, including neuropathy from etiology other than chemotherapy, such as diabetic neuropathy; (b) evaluated acupuncture for treatment of a condition unrelated to oncology; (c) available only in a language other than English; and (d), animal studies. Eighty-five abstracts were screened and 60 were excluded if (a) the article included multiple Complementary and Alternative Medicine (CAM) therapies without presence of an acupuncture specific treatment group or (b) the acupuncture protocol was integrated

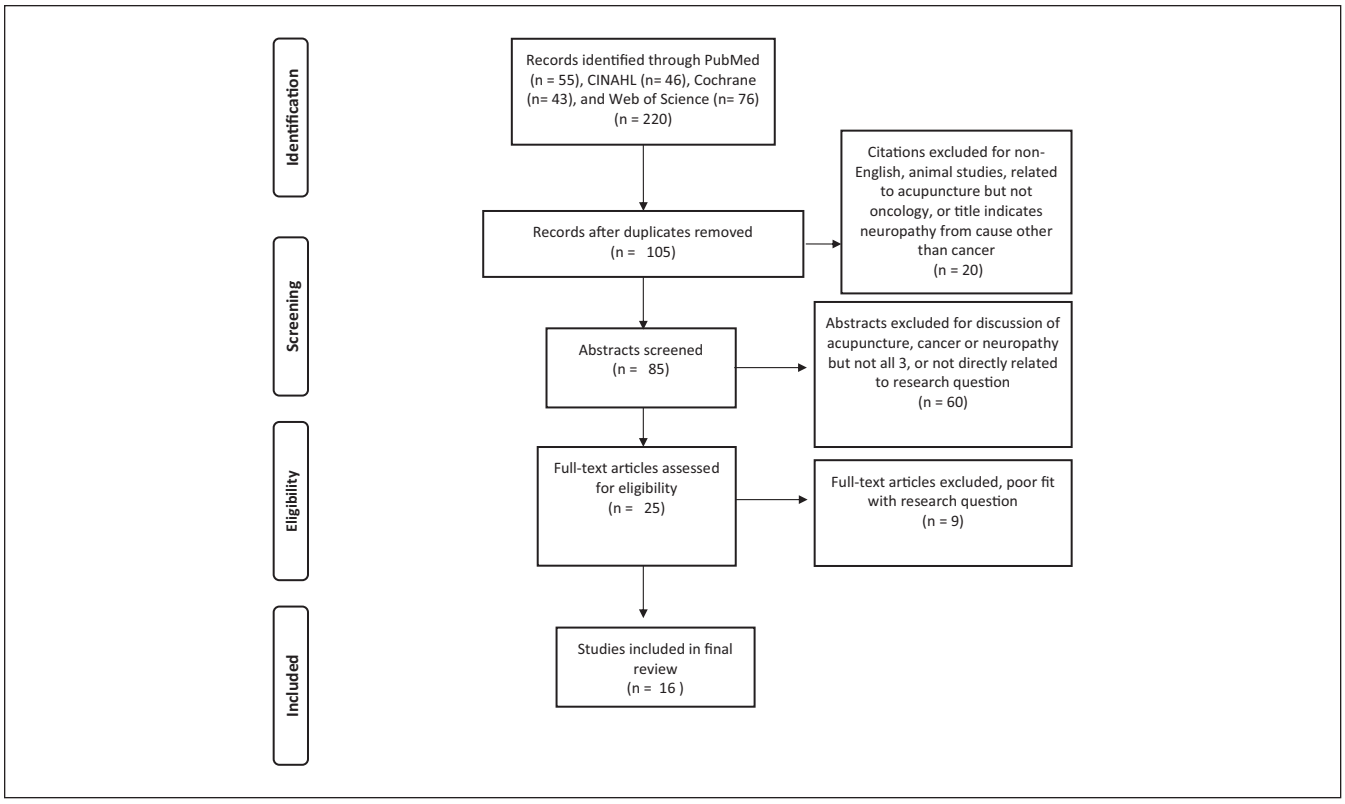

Figure 1. PRISMA Flow diagram describing search strategy and article selection.
Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7): e1000097. https://doi.org/10.1371/journal.pmed1000097.

with another therapy such as reflexology, lasers, or injectable medications or vitamins. The remaining 25 articles underwent a full text review. Following a full text review, 9 articles were removed due to poor fit with the research question, such as focusing on acupuncture for treatment of neuropathic pain in patients with cancer related to cause other than CIPN or if the study was a systematic review or meta-analysis versus a primary study. The final result included 16 articles, which were organized into a table to summarize key elements of the primary studies.

Results

The 16 studies included in the final review are summarized in Tables 1–3. The studies include 13 intervention studies, 2 retrospective chart reviews, and 1 case report.

Intervention Studies

Non-randomized/Quasi-experimental studies. Six studies involving small, single arm intervention trials are included in this review (Bao et al., 2014, 2018; Ben-Arye et al., 2018; Garcia et al., 2014; Jeong et al., 2018; Zhi et al., 2018). These findings include a diverse set of studies without a clearly consistent theme. Related to patient characteristics, five of the six studies included patients who had completed treatment (Bao et al., 2014; Ben-Arye et al., 2018; Garcia et al., 2014; Jeong et al., 2018; Zhi et al., 2018), with 1 study evaluating the effect of acupuncture on patients currently in treatment with chemotherapy (Bao et al., 2018). In all 6 studies, patients had varying levels of CIPN at study outset from mild to more severe. The aim of the study that involved patients in active treatment (Bao et al., 2018) was to evaluate the effectiveness of acupuncture to limit progression of symptoms from grade II to grade III CIPN.

A variety of acupuncture protocols were utilized, with most studies using acupuncture without EA on body acupoints (Bao et al., 2014, 2018; Jeong et al., 2018; Zhi et al., 2018) and 1 study involving EA (Garcia et al., 2014). Also, some studies included confounding variables making it difficult to ascertain the effect of acupuncture. For example, in Ben-Arye et al. (2018), the acupuncture technique was not defined and only 25% of the participants received an acupuncture-specific intervention that was not combined with another technique, such as touch or other unspecified mind-body therapy. In Garcia et al. (2014), 17 of the 19 participants used pharmacological therapy to treat CIPN in addition to acupuncture, including anticonvulsants and opioids.

Subjective and objective outcome measures varied among these studies. All 6 single-arm intervention studies

Table 1. Quasi-experimental Studies.

Authors/ Year	Purpose/ Aims	Sample	Intervention Description	Research Design	Outcome Measures	Results and Conclusions
Bao et al. (2018)	Determine efficacy of acupuncture to prevent progression from grade IIA to grade III CIPN in breast cancer patients receiving paclitaxel	27 women, ages 39–53 years, with stage I–III breast cancer	1–11 (median three total) weekly acupuncture treatments Acupuncture with *de qi* sensation per protocol Points used: Right ear shenmen & point zero, LI11, SJ5, LI4, St40, and bafeng	Single arm intervention study	Primary: Progression or absence of progression from grade II to grade III CIPN Multiple secondary outcomes listed, including: CIPN severity, measured by FACT-GOG/ Ntx and NPS scores, test of vibration with tuning fork	26/27 patients completed treatment without developing grade III CIPN Stable during continued treatment in all 27 patients No change in vibration test results
Bao et al. (2014)	Evaluate feasibility, safety and efficacy of acupuncture to treat neuropathy in patients who received bortezomib for multiple myeloma Explore possible mechanisms of action of acupuncture	27 patients with history of multiple myeloma who developed grade II or higher neuropathy following treatment with bortezomib	10 acupuncture treatments over 10 weeks including ear points shenmen, point zero and two additional points, and LI4, TE5, LI11, St40, and bafeng	Single arm intervention study	TNSc, FACT/GOG-NTx, and NPS Measurement of pro-inflammatory cytokines and neurotrophic factors NCS	TNSc results invalid Improvement in FACT/GOG-NTx and NPS No significant changes in in cytokines or neurotrophic factors No improvement in NCS
Ben-Arye et al. (2018)	Assess impact of acupuncture and complementary therapies on quality of life and function in women who had received taxanes for breast or gynecologic cancer	59 patient files, women age 18 years or older with breast or gynecologic cancer, who were treated with taxanes and received CIM therapy	All patients received acupuncture, 15 received acupuncture only, technique not described	Single arm intervention study	Patient narratives obtained from file and MYCAW (Measure yourself concerns and wellbeing) tool Four reviewers asked to assess narratives for impact of CIM on PN symptoms as: no, mild, or moderate benefit, or NA	35 patients received moderate benefit in neuropathy symptoms Effect of acupuncture to reduce symptoms noted by 17 patients
Garcia et al. (2014)	Evaluate safety, feasibility, and effectiveness of acupuncture to treat neuropathy in patients who received chemo-therapy for multiple myeloma	19 patients, 14 men and 5 women, mean age 64 years, with grade II–III peripheral neuropathy	20 acupuncture treatments over nine weeks Points: LI4*, SI3*, baxie, LV3*, Sp6, Gb42*, St36, bafeng, Du20, CV4, and CV6, with *de qi* and electrical stimulation on * points	Single arm intervention study	FACT/GOG-NTx, BPI-SF, FACT-G NCS Fall risk Timed function tests (coin test, walking, postural stability, fall and button test)	Scores improved in all patient reported outcome scales, greatest at week 9 No significant change in NCS Some improvement in fall risk Improved time function tests
Jeong et al. (2018)	Assess feasibility and safety of acupuncture for taxane-induced CIPN in Korean women	10 Korean women, ages 45–67 years, with CIPN grade I–IV following breast cancer treatment	12 acupuncture treatments, three times weekly for four consecutive weeks Manual acupuncture protocol, with points provided: LI11, LI4, St36, LV3, M-LE 8(bafeng), and M-UE 9(baxie)	Single arm intervention study	Neuropathy assessed with NPSI and NCS QoL assessed with SF-36 questionnaire	NPSI score reduced for all patients No significant change in NCS Improvement in several areas assessed by SF-36
Schroeder et al. (2012)	Assess ability of acupuncture to treat CIPN based on objective measures	11 male and female patients, mean age 65 years, who developed CIPN during chemotherapy	Six patients received acupuncture, and five provided control (based on refusal) 10 weekly acupuncture treatments Points used: St34, qiduan, bafeng, no *de qi* sensation	Quasi-experimental study	NCS Patient report of symptoms	NCS and patient report of symptoms improved after 6 months
Xiong et al. (2016)	Determine ability of acupuncture with injection of mecobalamin to treat symptoms of CIPN in women with breast cancer	90 women with breast cancer, ages 47 years to 71 years, with CIPN following treatment with taxanes or alkaloids	Patients received acupuncture, mecobalamin injection, or acupoint injection once every three days x 10 treatments Manual acupuncture protocol: LI 11, LI4, St26, Sp6, and Sp10 with manual stimulation	Randomized intervention study	EMG of ulnar and common peroneal nerve Observed changes in hemorrheology indicators	EMG measurements improved in all three groups, greatest in acupoint injection group Changes in hemorrheology indicators improved in all three groups, greatest in acupoint injection group
Zhang et al. (2017)	Assess effect of electro-acupuncture on QoL and immune status of patients with CIPN	37 male and female patients ages 36–79 years with malignancy and CIPN grade I–IV	18 received acupuncture, 19 electro-acupuncture Points: LI4 & LV3 with or without electro-acupuncture	Randomized intervention study	Primary: Peripheral neuropathy diagnosis according to grading system of Levi Secondary: TCM clinical symptoms Karnofsky performance status Immune function (NK cells, CD3, CD4, CD8. and CD4/CD8)	Improved in all categories except for immune function, where there was no effect Electro-acupuncture had a greater effect than acupuncture alone, with exception of immune function
Zhi et al. (2018)	Evaluate the impact of acupuncture on specific symptoms of CIPN in patients with bortezomib-induced neuropathy	27 patients with multiple myeloma who developed neuropathy grade II or higher following treatment with bortezomib	10 acupuncture treatments over 10 weeks Points included: ear points (shen men, point zero, and two additional points), LI4, TE5, LI11, St40, and bafeng with *de qi*	Single arm intervention study	FACT/GOG-Ntx and NPS	FACT/GOG-Ntx scores increased from baseline at week 14, indicating least neuropathy symptoms NPS scores reduced in all 10 areas, indicating improvement in neuropathic pain

Table 2. Randomized Studies.

Authors/ Year	Purpose/ Aims	Sample	Intervention Description	Research Design	Outcome Measures	Results and Conclusions
Greenlee et al. (2016)	Investigate the effect of electro-acupuncture to reduce or prevent CIPN in breast cancer patients treated with taxanes	63 women, ages >21 years, with stage I–III breast cancer	Patients randomized to receive either sham acupuncture or electro-acupuncture weekly for 12 weeks, within two days of weekly chemotherapy infusion Acupuncture protocol points: Gb34*, St36*, LI4*, LI10*, huatoujiaji points (at C5, C7, L3, and L5), bafeng, baxie (* = EA points)	RCT	BPI-SF FACT-NTX NPS-10 FACT-TAX Handheld bio-thesiometer to measure sensory neuropathy and pegboard test to measure motor-neurologic dysfunction	BPI-SF 1.62 greater in EA group vs sham at 16 weeks FACT-NTX trended toward increased pain at 16 weeks, without differences between groups NPS at 16 weeks EA group had worst pain No differences between groups in FACT-TAX, biosthesiometer, or grooved pegboard tests
W. Lu et al. (2019)	Evaluate ability of acupuncture to alleviate CIPN sensory symptoms in women treated with taxanes for breast cancer	40 women who had completed treatment with taxanes for breast cancer. Median time from end of treatment was 14 months.	18 acupuncture treatments over eight weeks. Manual acupuncture week 1, then EA Points used: yintang, LI11, TW5*, baxie*, Sp9, St36, Sp6*, Kd3, LV3*, and qiduan (* = EA points)	RCT	Patient report of symptoms measured by PNQ, FACT-NTX, BPI-SF, and QLQ-C30	35/40 patients completed the protocol Significant improvement in CIPN sensory symptoms, pain level, and QOL measures in intervention group
Molassiotis et al. (2019)	Assess efficacy of acupuncture to manage CIPN in cancer patients who had received or were currently receiving neurotoxic chemotherapy	Patients with breast, gynecologic, colorectal, head or neck cancer or multiple myeloma who had received neurotoxic chemotherapy with symptoms of CIPN	Patients randomized into wait-list control arm or acupuncture intervention arm Acupuncture points selected from a standardized pool of points at practitioner discretion: LI4, LI11, PC7, TE5, baxie, Sp6, St36, LV3, St41, and bafeng	RCT	Primary: BPI to measure pain Secondary: FACT/GOG-Ntx questionnaire to evaluate QoL with neurotoxicity specific module Symptom distress scale NCS	Pain improved in acupuncture arm vs control arm QoL significantly better in acupuncture arm vs control and neurotoxicity score also better in acupuncture arm No significant difference in NCS between groups
Rostock et al. (2013)	Evaluate role of electro-acupuncture in the manage-ment of CIPN	60 male and female patients with history of cancer in remission who developed CIPN following treatment with chemotherapy	Patients received electro-acupuncture, hydroelectric baths, high doses of vitamin B or a placebo Acupuncture treatments were eight sessions using pts: LV3, Sp9, Gb41, GB34, LI4, LI11, SI3, and Ht3 with electro-acupuncture	RCT	Primary: Patients interviewed on severity of CIPN, level of suffering, and to rate severity of symptoms Secondary: CIPN symptoms evaluated by neurologist including NCS QoL measured with EORTC QLQ-C30	Primary: Neuropathy scores improved in all groups Secondary: No significant differences in neurological assessment/NCS QoL moderately improved in all groups

Table 3. Retrospective Chart Reviews and Case Report.

Authors/ Year	Purpose/ Aims	Sample	Intervention Description	Research Design	Outcome Measures	Results and Conclusions
Donald et al. (2011)	Assess effective-ness of acupuncture to treat CIPN	18 male and female patients with neuropathy likely related to chemotherapy (comorbidities including DM and spinal metastasis listed for several patients)	17 patients received six weekly acupuncture treatments (one patient died during the study) Most common points used: Sp6, LV3, LI4, Bl60, St36, and bafeng/baxie	Retrospective study	Patient report of symptoms	82% reported improvement in neuropathy, 18% no change, no report of worsening symptoms Additional benefits reported: improved sleep, relaxation, stress, improved mood, less medication
Mandıroğlu et al. (2013)	Case study of patient who responded to acupuncture for neuropathy	One 74-year-old male patient with multiple myeloma, NPS 8/10	15 acupuncture treatments over 10 weeks Points used: St36, Sp6, and LI4 with de qi sensation	Case report	NPS scores during treatment and at 6 months following completion	NPS 0/10 at end of 15th treatment and at six months Reduction in symptoms of PN allowed for continued treatment with chemotherapy
Valentine-Davis & Altshuler (2015)	Report experience of the authors to treat and prevent CIPN in colorectal cancer patients who received oxaliplatin	10 patients with stage II–IV colon cancer	Acupuncture points selected based on TCM diagnosis of individual patient Relative aggressiveness of treatment regimen noted in terms of points selected and frequency of treatment	Retrospective study	End CIPN grade according to CTCAE v4.0 and patient response to acupuncture Acupuncture side-effects	Acupuncture resolved, improved or prevented progression in all patients There were no side-effects

found improvement in patient reported symptoms of CIPN, but no change in objective outcome measures. Subjective measures included Neuropathy Pain Scale (NPS) (Bao et al., 2014, 2018; Zhi et al., 2018), Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) (Bao et al., 2014, 2018; Garcia et al., 2016; Zhi et al., 2018), Brief Pain Inventory- Short Form (BPI-SF) (Garcia et al., 2014), and Measure Yourself Concerns and Well-being Tool (MYCAW) (Ben-Arye et al., 2018). Objective outcome measures included nerve conduction studies (NCS), also known as nerve conduction velocity test (NCV), in 2 studies (Bao et al., 2014; Garcia et al., 2014), and measurement of pro-inflammatory cytokines and neurotrophic factors in 1 study (Bao et al., 2014).

Schroeder et al. (2012) was a quasi-experimental study that included 11 participants who had developed CIPN following treatment with chemotherapy. This is the first known study in which NCS was utilized as an objective outcome measure. Six received acupuncture without EA. Five patients who refused the intervention provided the control group. Effect of the acupuncture was measured by patient self-report and NCS. Both patient report of symptoms and NCS were improved after six months.

Randomized studies. Four RCTs are included in this review: Greenlee et al. (2016); Lu et al. (2019); Molassiotis, Suen, et al. (2019); and Rostock et al. (2013). The studies included patients currently in treatment (Greenlee et al., 2016) and post-treatment survivors (Lu et al., 2019; Rostock et al., 2013). Molassiotis, Suen, et al. (2019) included both patients actively in treatment and post-treatment survivors. Three studies used EA (Greenlee et al., 2016; Lu et al., 2019; Rostock et al., 2013). Greenlee et al. (2016) evaluated the effects of EA for patients currently in treatment using a variety of acupoints including distal extremity points *bafeng* and *baxie*. Rostock et al. (2013) was a four-arm trial evaluating EA, hydroelectric baths, high doses of vitamin B, or a placebo concurrent with other therapies including massage and relaxation therapy in survivors. The acupuncture protocol used in Lu et al. (2019) involved one acupuncture treatment without EA followed by EA in 40 breast cancer survivors.

Subjective outcome measures utilized in the four RCTs include BPI (Molassiotis, Suen, et al., 2019), or BPI-SF (Greenlee et al., 2016; Lu et al., 2019), FACT-Ntx (Greenlee et al., 2016; Lu et al., 2019; Molassiotis, Suen, et al., 2019), NPS (Greenlee et al., 2016), Quality of Life Questionnaire (QLQ-C30) (W. Lu et al., 2019; Rostock et al., 2013), and patient report of symptoms (Rostock et al., 2013). Objective outcome measures assessed included handheld biothesiometer (Greenlee et al., 2016), pegboard test (Greenlee et al., 2016), and NCS (Molassiotis, Suen, et al., 2019; Rostock et al., 2013). Greenlee et al. (2016) reported worsening pain at 16 weeks as measured by NPS, with no difference in objective measures. The other three studies (Lu et al., 2019; Molassiotis, Suen, et al., 2019; Rostock et al., 2013) indicated improvement in subjective outcome measures. In the study by Rostock et al. (2013), participants in all four arms of the study reported improvement in neuropathy scores and quality of life; there was no improvement in objective outcome measures including NCS, biothesiometer, and pegboard test.

Xiong et al. (2016) randomized 90 women who had developed CIPN following treatment for breast cancer into one of three treatment arms, which included acupuncture, mecobalamin injection without acupuncture, or acupoint injection with mecobalamin. Outcomes assessed included patient symptoms, EMG measurements, and changes in hematological indicators. This study found that the outcome measures were improved in all groups, with the greatest improvement in the group that received acupoint injection.

Zhang et al. (2017) randomized 37 male and female participants with baseline CIPN grade I-IV to receive either acupuncture or EA concurrent with treatment with chemotherapy. Only two acupuncture points, LI4 and LV3, were used in both the acupuncture and EA groups. Outcome measures included a diagnosis of neuropathy based on the grading system of Levi, TCM clinical symptoms, Karnofsky performance status, and immune function indicators. The authors note an improvement in all outcome measures with the exception of immune function indicators, with greater improvement in the EA group than the manual acupuncture group.

Retrospective Chart Reviews

Two retrospective studies are included in this review. Donald et al. (2011) reviewed the charts of 18 patients with neuropathy who had received chemotherapy and acupuncture without EA. The authors note that several of the patients had other medical conditions known to cause neuropathy, including diabetes and spinal metastases. Patient report of symptoms were obtained and revealed that fourteen patients (82%) reported improvement in neuropathy symptoms, while three reported no change or worsening symptoms. One patient died prior to completion of the study. However, no baseline measurements of CIPN were available/obtained.

In the study by Valentine-Davis & Altshuler (2015), the charts of 10 patients who had received oxaliplatin for colorectal cancer and different combinations of acupuncture treatments were reviewed, including persons currently in treatment and survivors. Not all of the acupuncture treatments are described in detail, however the authors state that the patients received a range of treatments in terms of aggressiveness, which they define by acupuncture points selected and frequency of the treatments. All of the patients had some improvement in symptoms of CIPN, based on health care provider report. Two of the patients had a dose reduction in their chemotherapy, the implications of which are not discussed.

Case Report

A case report (Mandıroğlu, et al., 2014) followed a 74-year-old patient with CIPN symptoms while receiving bortezomib for multiple myeloma. The patient received 15 acupuncture

treatments. His pain was assessed using NPS, which was 0/10 at the end of the last acupuncture treatment at six months. The authors report that the reduction in patient symptoms supported the patient to continue his chemotherapy.

Discussion

This paper makes an important scientific contribution through a more comprehensive review of the literature on the ability of acupuncture to treat CIPN. Prior literature reviews by Baviera et al. (2019), Chien et al. (2019), and Li et al. (2019) selected a smaller range of studies based on narrower exclusion criteria such as the definition of acupuncture or the study design. This integrative review reveals that, overall, the available evidence is limited to studies characterized by small sample sizes, heterogenous design, and variable outcome measures. A variety of acupuncture techniques and protocols were used to evaluate the effectiveness of acupuncture to treat CIPN and, with the exception of Greenlee et al. (2016), found at least some improvement in subjective outcome measures without corresponding improvement in objective measurements. As the evidence demonstrates that patients who receive acupuncture generally report subjective improvement in symptoms of CIPN without improvement in objective measures, the question arises as to whether new objective measures need to be developed, or if the emphasis of evaluation should be patient report of pain and quality of life indicators.

The need to establish consistent and clinically relevant measures to evaluate the impact of acupuncture on quality of life for patients with CIPN is discussed in the review by Baviera et al. (2019). Therefore, evaluating acupuncture through a more pragmatic lens that focuses on effectiveness, including impact on pain and quality of life, may prove more meaningful than establishing efficacy as measured by improvement in controlled clinical settings (Ang & Kaptchuk, 2011; Kaptchuk et al., 2010). In sum, main themes and recommendations for future research identified by this integrative review of the literature include (a) the need for a consistent definition of acupuncture as an intervention; (b) the need to develop standardized acupuncture protocols; and (c) the need for consistent outcome measures and comparison treatments to evaluate the benefit of acupuncture for CIPN. Each of these themes is discussed in detail further.

In order to optimally evaluate the effectiveness of acupuncture, consensus is needed on what technique, or group of techniques, is being evaluated when the term "acupuncture" is used. Comparison of the prior reviews by Baviera et al. (2019), Franconi et al. (2013), and Li et al. (2019) demonstrates the need for a consistent definition of acupuncture as a technique. For example, Baviera et al. (2019) included only acupuncture studies that involved manual acupuncture without the use of auricular acupuncture, laser, or EA. Franconi et al. (2013) included any studies involving acupuncture needling of humans or animals with the addition of auricular acupuncture and EA. Li et al. (2019) defined acupuncture in even broader terms to include any use of acupuncture, EA, or acupressure as a primary or adjunctive therapy.

Excluding studies of acupuncture that involve auricular acupuncture or EA would have eliminated several studies of importance in this review (Bao et al., 2014; Garcia et al., 2016; Greenlee et al., 2016; Z. Lu et al., 2017; Rostock et al., 2013; Xiong et al., 2016; Zhang et al., 2017). EA is used in 5 of the included studies (Garcia et al. 2016; Greenlee et al., 2016; W. Lu et al., 2019; Rostock et al., 2013; Zhang et al., 2017), indicating that this technique is considered important and should be evaluated for its effectiveness in clinical practice for the management of CIPN. This review utilizes a definition of acupuncture similar to that of the search performed in the meta-analysis by Chien et al. (2019), which included studies of true needle acupuncture or EA while excluding techniques that did not involve acupuncture needles such as laser techniques. Defining acupuncture to include studies in which it is used as an adjunctive to other therapies could obscure the effects of the acupuncture intervention. A definition of acupuncture that includes use of true needle acupuncture on the body, auricular acupuncture, and EA provides a comprehensive view of the use of acupuncture in clinical practice while minimizing non-acupuncture techniques such as lasers or injections into acupoints.

Another area for improvement identified by this review of the literature is the need to develop standardized acupuncture treatment protocols. The literature indicates that acupuncture treatment protocols for management of CIPN should be based upon whether patients are currently in treatment or are post-treatment survivors. Patients receiving active treatment with neurotoxic chemotherapy may benefit from a comparatively less aggressive acupuncture treatment approach, as defined by factors including the location of points used, frequency of treatment, and inclusion of EA. Aggressive treatment protocols and EA may have more effectiveness in the management of CIPN for post-therapy survivors.

In addition to consideration of active versus post-therapy treatment status, this integrative review found evidence to support the use of specific treatment points for patients with CIPN. According to diagnostic criteria of TCM, patients with cancer are generally characterized as having what is referred to as "deficiency" in several areas (Lu et al., 2017; Valentine-Davis & Altshuler, 2015). While TCM practice emphasizes the need to develop individualized patient treatment plans, the literature suggests that even more tailored and effective point protocols could be developed that reflect TCM principles such as avoidance of more aggressive treatments in deficient patients. For example, the majority of studies included local treatment points on the hands and feet, and nearly all of these studies were associated with improvement in patient report of CIPN symptoms. Additionally, Chien et al. (2019) suggested that acupuncture may be more

effective for CIPN related to the specific type of chemotherapy received, noting a positive effect of acupuncture for patients who developed CIPN following treatment with bortezomib.

Lack of objective outcome measures of CIPN that correlate with patient report of improved symptoms is also a limitation noted in the systematic review by Baviera et al. (2013) and meta-analysis by Chien et al. (2019). NCS was used as an outcome measure in several studies (Bao et al., 2014; Garcia et al., 2014; Molassiotis, Suen, et al., 2019; Rostock et al., 2013) following Schroeder et al. (2012), a study in which patient report of improvement in symptoms did correlate with results of NCS. Of note, only 6 of 11 total patients received the acupuncture intervention in Schroeder et al. (2012). In all of these subsequent studies of acupuncture for CIPN, change in NCS did not correlate with patient report of symptoms.

Ability to determine objective measurements of the effects of acupuncture in the treatment of CIPN is complicated by the fact that recent studies have highlighted inadequacies of current methods of CIPN assessment (Molassiotis, Cheng, et al., 2019). NCS has been used as an outcome measure in studies of acupuncture for nerve pain related to other etiologies such as carpal tunnel (Maeda et al., 2017), however NCS may not be an effective measure of effects acupuncture on nerve damage related to other etiologies including neurotoxic chemotherapy. Motor function tests such as timed function tests may be of more benefit to demonstrate effects of acupuncture on CIPN symptoms. While NCS may not be the most reliable objective measure of acupuncture in the treatment of CIPN, other methods including timed function tests and other assessments of motor symptoms could prove to have more value.

Further work to identify appropriate and consistent measures to evaluate the efficacy of acupuncture for patients with cancer is important to advance symptom science. Different outcome measures may be indicated based upon factors such as the patient's goals of care and whether they are receiving chemotherapy or other potentially neurotoxic therapy. For many patients, subjective improvement in their pain and quality of life, including such factors as mobility or sleep, versus objective measures including NCS, may reflect a more meaningful impact of acupuncture on symptoms of CIPN. In addition to developing appropriate and consistent outcome measurements, future research should seek to explore more thoroughly the potential effects of acupuncture on the overall quality of life of patients coping with CIPN through in-depth qualitative research.

The primary limitation of this integrative review is the small number of studies on acupuncture in the management of CIPN published in the past 10 years that met inclusion criteria. Risk of bias in the primary studies including lack of random assignment is an additional limitation related to the existing research. Some studies were only available in languages other than English, most notably Chinese; budgetary constraints precluded our ability to translate Chinese language studies into English for consideration, which further limited the sample size. An additional limitation is that the grey literature was not included in the search.

CIPN is a condition associated with both pain and decreased quality of life which affects an estimated 30%–40% of patients with cancer. This integrative review regarding acupuncture for the treatment of CIPN in patients with cancer revealed gaps in the current body of literature that make it difficult to evaluate its impact, including small sample sizes and variability in study design. By evaluating 16 studies in which acupuncture was the primary intervention in the treatment of CIPN, several themes were identified. First, a clear and consistent definition of which technique, or group of techniques, is considered acupuncture is needed for use across the literature. This review proposes a definition of acupuncture that includes needle insertion into body and auricular acupoints, with the addition of EA. A second theme is the need to establish standardized acupuncture protocols for treatment of CIPN, such as those that include local points on the hands and feet. More aggressive point combinations and potentially also EA may be of more benefit for post-treatment survivors than those still in active treatment with neurotoxic chemotherapy. Finally, more research is needed to establish consistent and clinically relevant outcome measures to evaluate the effects of acupuncture on pain and quality of life in patients with CIPN.

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