

SOUTH BAYLO UNIVERSITY

**The Effectiveness of Acupuncture for the Treatment of Peripheral
Neuropathy Due to Diabetes and Chemotherapy: A Narrative Review**

By

Dimitri Gruer

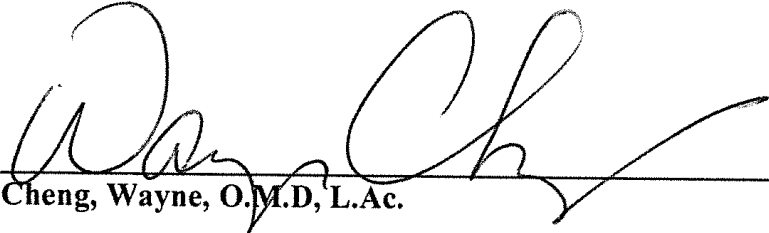
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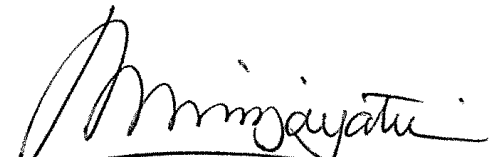
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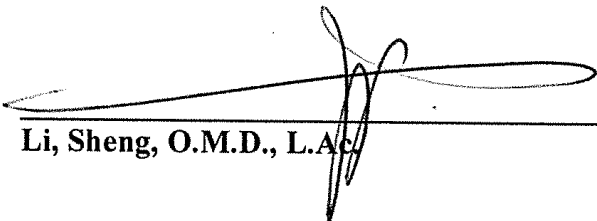
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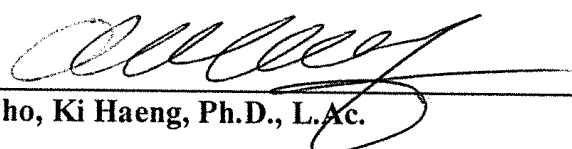
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**The Effectiveness of Acupuncture for the Treatment of Peripheral Neuropathy Due
to Diabetes and Chemotherapy: A Narrative Review**

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SOUTH BAYLO UNIVERSITY AT ANAHEIM, 2018

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ABSTRACT

Peripheral neuropathy (PN) is one of the most common and debilitating symptoms present in some of the most prevalent systemic diseases found in today's society, including but not limited to diabetes mellitus, autoimmune disorders, HIV related complications and cancer related therapies. Due to its increasing statistical fortitude within the United States as well as the growing incidences in the rest of the developing world, safe and effective treatment methods used to treat PN must be researched thoroughly and extensively in order to quell this current detrimental epidemic. The purpose of this review is to determine if acupuncture is an effective treatment method for treating two of the most common causes of PN, diabetic peripheral neuropathy (DPN) and chemotherapy induced peripheral neuropathy (CIPN). The design of this review is to explore the mechanisms of both PN and acupuncture, explain the current limitations in research on acupuncture, and present, analyze and compare past trials on the subject. After using three online search databases of published research, ten studies including

randomized control trials, single-arm studies and retrospective studies on acupuncture for DPN and CIPN were identified as containing relevant information for analyzation. While positive evidence on acupuncture's effectiveness was observed in the majority of the studies, the limitations found due to the lack of standardization regarding control methods, treatment protocols and sample sizes precludes any evidence that acupuncture is effective for treating PN in any of its forms. However, due to the positive results, future larger-scale studies with standardized protocols is warranted as acupuncture is a safe, low-risk alternative to current treatment methods that have not been found to be effective long term.

Keywords: Peripheral Neuropathy, Diabetic Peripheral Neuropathy, Chemotherapy Induced Peripheral Neuropathy, Acupuncture, Acupuncture Mechanism

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I. INTRODUCTION

According to the National Institute of Neurological Disorders and Stroke, more than 20 million people in the United States have been estimated to present with some form of peripheral neuropathy (NINDS, 2018). The overall prevalence is approximately 2,400 (2.4%) per 100,000 people, but in individuals older than 55 years, it rises to approximately 8,000 (8%) per 100,000 (Merkies, Faber, and Lauria, 2015). Due to the widely varying and complex nature of PN, these figures may be significantly higher from lack of reporting. While an individual may present with certain sensations that a medical professional would diagnose as PN based upon their overall medical history, the patient may not report it due to a lack of understanding of what is a clinically relevant symptom that would help in their diagnosis.

The severe primary disorders that typically lead to peripheral neuropathy present a complex range of symptoms from both the main disease and secondary side-effects from their modern treatment models. Given this complexity, there is not a single, unifying treatment method that has been found to treat all of the presentations in a clear and effective manner. While there are preferred pharmacological treatments for common presentations of PN, such as Gabapentin for DPN (Moore, Derry, Wiffen, 2018), there is no standard treatment intervention that has been found to be successful across all causes of PN.

The purpose of this review is to examine if acupuncture is a safe and effective alternative treatment method for treating any of the various forms of peripheral

neuropathy with a primary focus on two of the most common causes, diabetic peripheral neuropathy (DPN) and chemotherapy induced peripheral neuropathy (CIPN).

Classification and Mechanism of PN

Common clinical descriptions of PN can be classified based upon their affected nervous systems. Sensory symptoms include, but are not limited to numbness, tingling, weakness, burning, stabbing or electrical sensations. Less commonly discussed are autonomic system dysfunctions such as early satiety, impotence, orthostatic hypotension, and sweat abnormalities (Watson and Dyck, 2015).

There are three pathological mechanisms in which neuropathies affect the peripheral nervous system: axonal degeneration, segmental demyelination, and neuronopathy. Axonal degeneration is the most common pathology seen in systemic, metabolic, toxic, and nutritional disorders. It characteristically has a predilection for large diameter and long fibre-distal axonopathy or dying back neuropathy. Segmental demyelination is primary destruction of the myelin sheath leaving the axon intact, although axonal degeneration may also be present in demyelinating neuropathies and secondary segmental demyelination may be seen in axonal degeneration. Neuronopathies are those conditions in which the cell bodies of axons-anterior horn cells or dorsal root ganglia are primarily affected (McLeod, 1995).

PN develops as a combination of just six primary mechanisms: altered metabolism, covalent modification, altered organelle function and reactive oxygen species formation, altered intracellular and inflammatory signaling, slowed axonal transport, and altered ion

channel dynamics and expression. All of these pathways converge to lead to axon dysfunction and symptoms of neuropathy (Cashman and Hoke, 2015)

Epidemiology and Cost

DPN is the most common cause of PN (Javed, Petropoulos, and Alam, 2015). The prevalence of neuropathy in patients with diabetes is approximately 30%, with up to 50% eventually developing neuropathy during the course of their disease (Callaghan, Chang, and Stables, 2012). The global statistics of diabetes mellitus in 2013 indicated about 382 million people had the disease worldwide (Tao, Shi, and Zhao, 2013) with estimated annual costs averaging between 612 to 1,099 billion USD (Fernandez, Ogurtsova, Linnenkamp, 2016). In regard to individual cost, total average annual direct medical costs in the US in 2014 were \$12,492 for DPN, \$27,931 for painful DPN and \$30,755 for severe painful DPN (Sadosky, Mardekian, and Parsons, 2014).

PN is one of the greatest and most prevalent adverse effect from most chemotherapy agents affecting already vulnerable patients suffering from cancer. In broad terms, around two-thirds of patients will suffer from CIPN in the first month after chemotherapy, but in only one-half of these will CIPN have resolved by six months. CIPN, across all forms, was observed in 68.1%, 60%, and 30% of patients, within the first month, at three months, and at six months respectively (Seretny, Currie, Sena, 2014).

Current Treatment Methods

Many RCTs have investigated potential therapies for the prevention of CIPN development or reversal of established CIPN. However, clinical practice guidelines from the American Society of Clinical Oncology after a systematic review did not recommend any agent for the prevention of CIPN. Thus, treatment of CIPN is mainly based on evidence from other chronic neuropathic pain conditions, rather than specifically targeting underlying mechanisms in CIPN (Flatters, Dougherty, and Colvin, 2017). Given this fact, the following treatment options more commonly used for DPN can also be correlated to modern treatments used by clinicians for CIPN.

According to Snyder, Gibbs, and Lindsay (2016) in their review on current treatment methods for DPN, interventions should be chosen and disseminated based upon their pharmaceutical category. After initial patient evaluation, the first-line therapies are anticonvulsants and tricyclic antidepressants; second-line therapies are serotonin-norepinephrine reuptake inhibitors (SNRIs), opioid-like drugs and topical medications; and third-line therapy are selective serotonin reuptake inhibitors (SSRIs) and opioids (figure 1). The long-term safety of most agents used to treat painful DPN has not been well-established. Safety and efficacy data from studies of more than 14 weeks specific to patients with painful DPN have not been published for TCAs, pregabalin, gabapentin, or opioids (Ziegler and Fonseca, 2015).

Modern treatment method chart

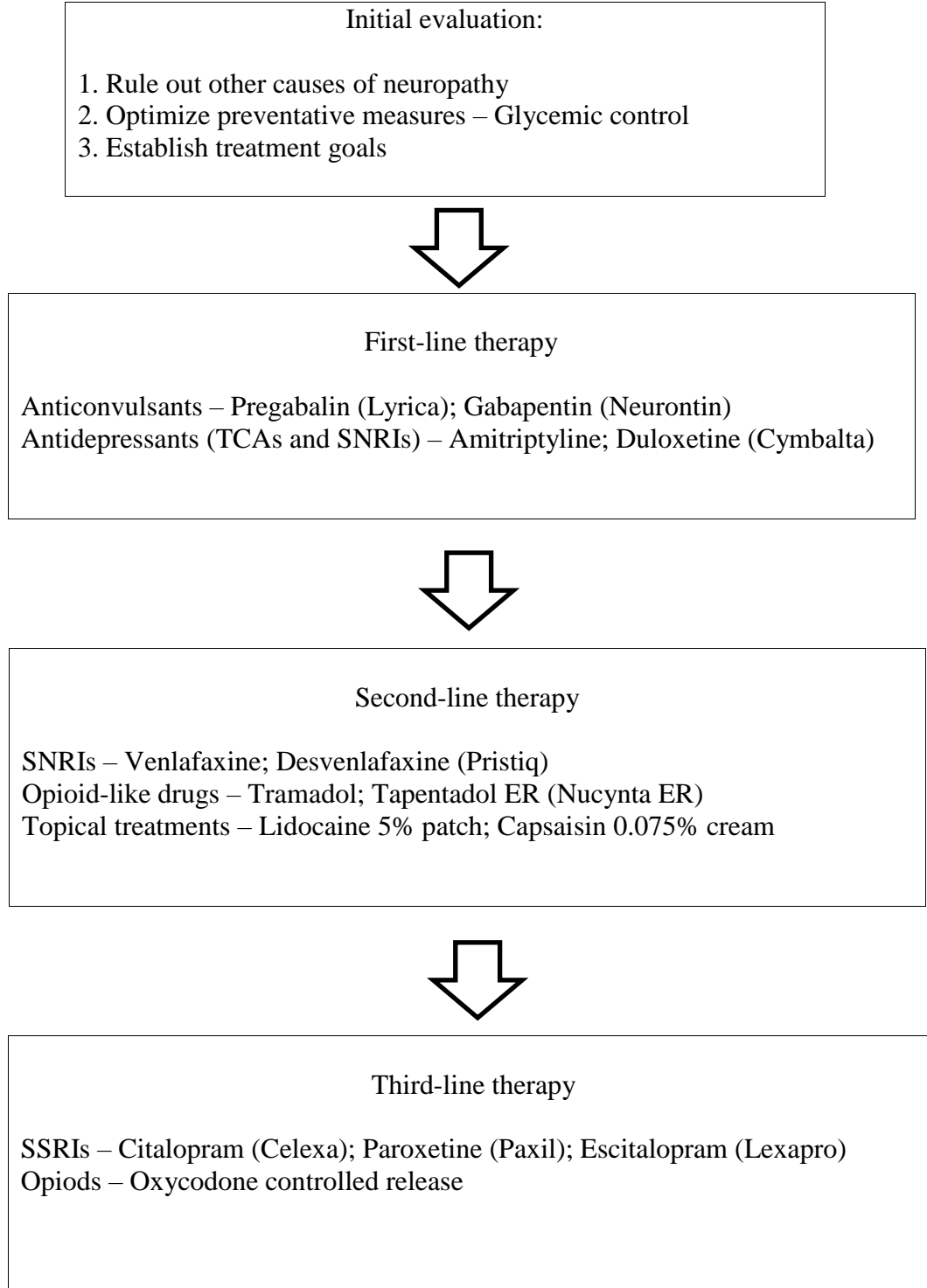


Figure 1. Management of Painful Diabetic Peripheral Neuropathy, Snyder et al. (2016)

The anticonvulsant medication gabapentin (Neurontin) is currently the most common prescribed pharmaceutical agent for treating PN. According to Moore et al. (2018), oral gabapentin (1200-3600 mg/d) was associated with greater improvement in people with moderate or severe DPN compared to placebo. (38% efficacy for pain intensity reduction of $\geq 50\%$ and 52% efficacy for pain intensity reduction of $\geq 30\%$; compared to 21% and 37% for placebo respectively). Common adverse effects from taking gabapentin are somnolence, dizziness, diarrhea, headache, nausea, and confusion (Lindsay, Rodgers, Savath, 2010).

Acupuncture in Research

Acupuncture is a form of complementary alternative medicine (CAM) rooted in Traditional Chinese Medicine (TCM) in which fine metal needles are inserted into the body at specific points to produce a therapeutic effect. Its effectiveness in terms of reliable, clinical data has struggled in finding definite positive results using evidence-based research, which is the fundamental cornerstone of what would allow a medical modality to become fully utilized in the Western healthcare system. This may be due to the differences in how Western and Eastern medicine approach scientific questions. Western medicine is based upon the hypothesis method while Eastern medicine uses the inductive method. The hypothesis is usually derived from general observations of a phenomenon and a research plan is carefully designed. When enough data are collected, conclusions are drawn as a result of critical statistical evaluations. The inductive method starts with many observations of nature, with the goal of finding a few, powerful

statements about how nature works. Oriental medical literature in general is a record of practical experience accumulated from practitioners throughout thousands of years. The format of recording is a result of direct observation (Tsuei, 1978). Given these fundamentally different approaches to confirming efficacy through treatment, new rational techniques in integrating acupuncture into evidence-based research must be developed.

A prime example of the difficulty in obtaining clinically relevant results for acupuncture's efficacy was explored by Chen, Yang, Liu (2013) in a systematic review of RCTs on DPN in China. In their review, they included 25 trials both published and unpublished involving 1,649 participants. Despite the high number of trials and what they describe as uniformly positive results, the study concluded that no clinically relevant conclusions could be drawn due to the trials' high risks of bias and the possibility of publication bias. Their solution to the problem they observed was to properly train Chinese researchers in conducting unbiased trials as well as prospectively registering all initiated Chinese trials to avoid publication bias.

Practitioners of acupuncture believe that the medicine is individualistic with results varying from person to person based on many factors including not only the state of the patient's health, but also the practicing style of the practitioner, of which there are many. A strong disconnect between Western and Eastern treatment models lies within how they diagnosis disease. For example, in conventional medicine, an individual presenting with PN who has diabetes is simply given a diagnosis of PN due to complications from diabetes, necessitating pharmaceutical intervention to manage the symptom. From the viewpoint of TCM, the etiology and pathogenesis of the disease follows a pathway as

follows: (1) with an increased duration of disease in diabetes, a deficiency of yin burns body fluid and blood, resulting in empty heat. This increases blood viscosity, resulting in blood stasis, as well as blockage of sinews and channels; (2) excessive intake of foods high in fat and sugar content results in the deficiency of spleen and stomach, resulting in the accumulation of dampness and phlegm, which has a synergistic effect with stasis; (3) sinew and channels demonstrate poor nourishment because of the deficiency of liver and kidney; (4) the deficiency of yin results in a deficiency of yang, which generates an inner cold that results in microvascular coagulation. These four aspects result in a decreased peripheral flow of qi and blood to muscles, sinews, and channels. The root cause is deficiency in qi, yin, and yang; the subsequent complication is blood stasis and phlegm accumulation (Piao and Liang, 2012). This leads to complications in unifying conclusive results within research based studies on acupuncture because study participants might be chosen based on one single western diagnosis i.e. DPN; when there are multiple possible diagnoses and treatment protocols in TCM that would need to be specifically tailored to the individual's current condition. For this reason, in addition to data from clinical trials, information regarding the known scientific mechanisms of how acupuncture works is paramount in understanding how acupuncture can be logically interpreted to treat PN in a clinical setting.

Acupuncture Mechanism

The specific mechanism of how acupuncture works on regulating pain through both the central nervous system (CNS) and peripheral nervous system (PNS) has not been

fully realized; however, there are two current theories that help explain the possible functions in treating various forms of neuropathy. The peripheral mechanism theory suggests that acupuncture can excite pressure on stretch receptors in tissues around the acupuncture point. Acupuncture stimulation is converted into nerve impulses by these receptors and the impulses are transmitted through fibers II and III. The central mechanism theory suggests that acupuncture impulses transmitted to the CNS will activate the brainstem descending inhibitory system, mesolimbic analgesic circuits, forebrain circuits and dorsal raphe nucleus-parafascicular pathway of the endogenous pain modulation system. The impulses will also affect the endogenous opioid peptides and single amine neurotransmitters and interact with nociceptive afferent signals at different levels of the CNS to inhibit the transmission and expression of nociceptive information and achieve the analgesic effect (Zhao, Rong, and Shi, 2014).

According to Zhang, Lao, and Ren (2014), the mechanism for electro-acupuncture (EA) is that it mitigates pain by up-regulating endogenous anandamide, which activates CB2R to promote opioid production. Peripheral opioids play a central role in EA's inhibition of inflammatory pain by blocking pro-inflammatory cytokine release from polymorphonuclear leukocytes and mononuclear cells and by acting on peripheral opioid receptors to desensitize peripheral sensory nerves (figure 2).

Nervous system pathways activated by acupuncture with possible beneficial effects of acupuncture in CIPN patients

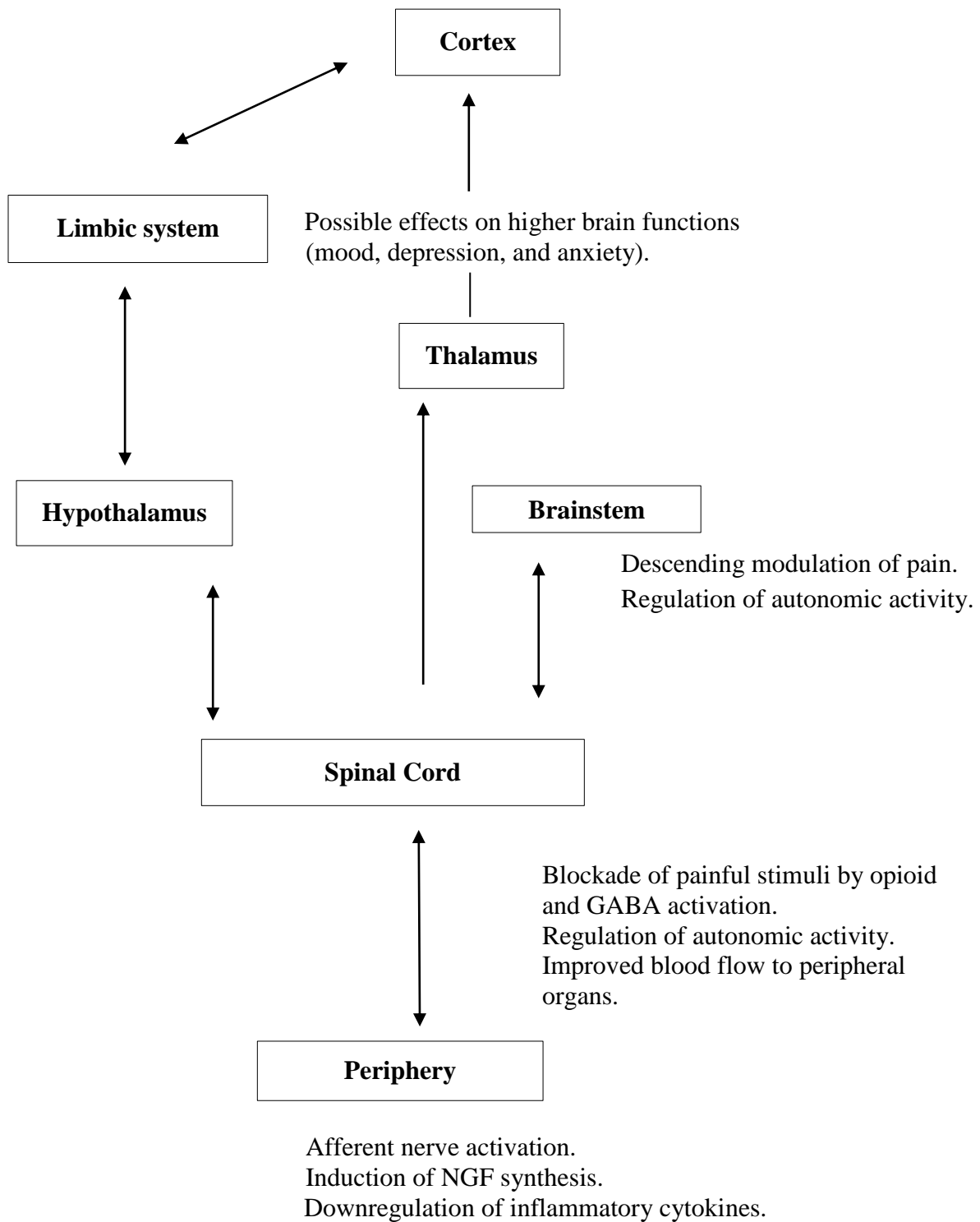


Figure 2. Nervous System Pathway Activation by Acupuncture, Franconi et al. (2013)

The theoretical basis of what acupuncture attempts to achieve through treatment is a homeostatic effect. The fundamental cause of disease within conditions such as diabetes and cancer is essentially a lack of balance within the body. Diabetes is caused by a hormone system imbalance in which the essential hormone insulin cannot be properly utilized to control blood glucose levels. Cancer is an imbalance of the DNA within cells in which irregular, mutated cells are unable to be destroyed by immune cells and are able to proliferate. Given this common link within disorders such as diabetes and cancer, the primary goal of acupuncture therapy is to reverse disease by stimulating the body's natural healing mechanisms through activation of the CNS/PNS and endocrine systems to promote balance. By treating the root cause of the imbalance in addition to the symptoms, the potential for therapeutic effect with minimal side-effects should be greater in achieving long-term results in comparison to pharmaceutical interventions aimed primarily at symptom management.

II. MATERIALS AND METHODS

1. Literature Search

Three primary electronic search databases were used to find research literature on the proposed topic: PubMed, the Cochrane Central Register of Controlled Trials, and EBSCO. An initial search for keywords of “peripheral neuropathy AND acupuncture” was made using a full text filter leading to 380 results. Supplementary searches included the keywords “peripheral neuropathy AND acupuncture AND diabetes OR diabetic peripheral neuropathy OR DPN” as well as “peripheral neuropathy AND acupuncture AND chemotherapy OR CIPN,” “acupuncture mechanism” and “peripheral neuropathy mechanism.” Results pertaining to diabetes led to 74 results, while results for chemotherapy produced 132 results. After eliminating duplicate and irrelevant sources, 5 trials pertaining to DPN and 3 trials on CIPN were identified as relevant for evaluation and comparison. The design of 5 of the studies were randomized control trials (RCT), while the other 3 were based on evaluative research. In addition, 2 retrospective studies on CIPN were identified as relevant, but have been separated from the 8 primary trial evaluations since the research was not performed in a uniform manner (figure 3).

2. Inclusion and exclusion Criteria

Inclusion criteria was established as any trials performed after year 2000 in which the primary area of study was for acupuncture and the treatment of PN with an emphasis on

either DPN or CIPN. The types of acupuncture included were set as manual type acupuncture and/or EA. RCTs and evaluation studies based on objective and subjective findings were included for analyzation.

Exclusion criteria was set at studies and reviews prior to year 2000, sources not attainable in full text, opinion based articles and non-peer reviewed articles, singular case studies and research not found in English. Laser and bee venom type acupuncture studies were also excluded as well as acupuncture studies performed on animals.

3. Data Extraction and Analysis

The data extracted for each study were the condition(s) evaluated, sample size, treatment method, control groups, acupuncture points used, treatment time, frequency, average treatments performed per week, and outcomes. These methods were analyzed by comparing and contrasting the measurable outcomes based on statistical significance and similarities between types of assessment tests and control groups.

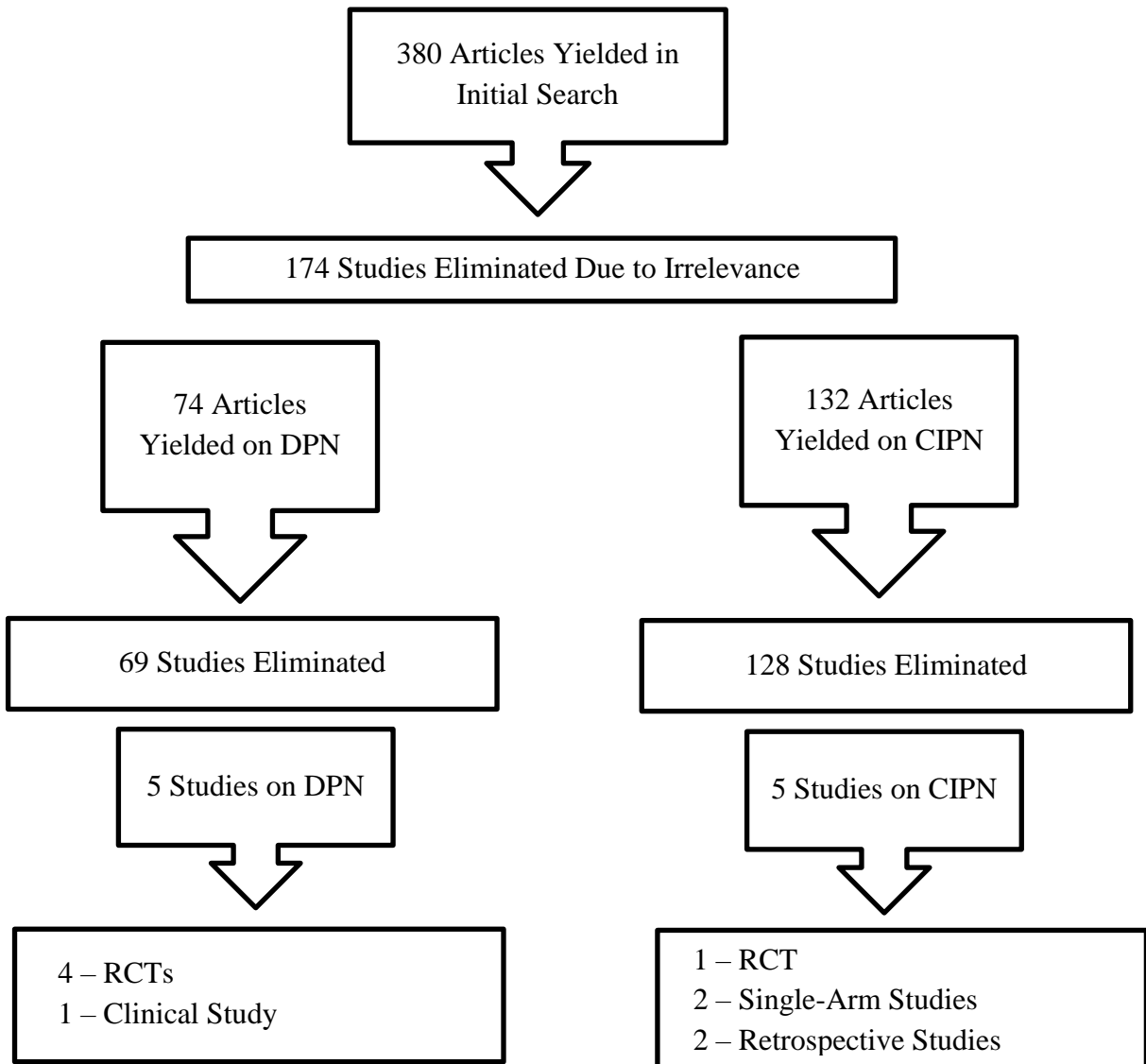


Figure 3. Flow Chart of Study Selection

III. RESULTS

#1 RCT on DPN (Zhang, Ma, and Yan, 2010)

In a RCT from China in 2010, a study on patients with PN due to diabetes complications was performed by splitting 65 patients randomly into two groups. The treatment group consisted of 32 patients that were given acupuncture treatments once a day, with 14 sessions as one course of treatment, for 5 consecutive courses with a 4-day interval between courses. The other 33 cases in the control group were given 2g of Inositol 3 times a day. The criteria for therapeutic effect was established as markedly relieved, improved, or failed. Markedly relieved meant the subjective symptoms disappeared with no abnormalities found in examination of the nervous system. Improved indicated the subject's symptoms were alleviated or the affected area was reduced, with improvement shown by the nervous system examination. Failed indicated no improvement or aggravation of the subjective symptoms. The results for the treatment group were 16 cases markedly relieved, 12 cases improved, and 4 cases failed for a total effective rate of 87.5%. The control group results had an effective rate of 63.6%, with a significant difference in the total effective rate between the two groups ($P<0.05$).

Table 1. Summary of Zhang, Ma, and Yan, 2010

Research Design	RCT
Participants	Sample size: 65 = 32 in treatment group, 33 in control group
Interventions	Acupuncture, 70 total treatments, Table 10 for acupoints
Comparison	Control group: Inositol – 2g 3x/day
Outcomes	Total effective rate: 87.5% vs 63.6% in control group ($P<0.05$)

#2 RCT on DPN (Zheng, Yuan, and Zhang, 2004)

In another RCT from China, a study was established to test acupuncture's effectiveness on 104 patients with DPN. The therapeutic method of the study was to determine if acupuncture plus a combination of a drug, was effective for treating DPN vs. a control group of mecobalamin. The 52 patients in the treatment group were given acupuncture with a 2 ml injection of Snow Lotus. The treatments were performed three times per week every other day for a total of 20 treatments per patient. The control group was given 500 µg of mecobalamin 3 times a day for 2 consecutive months. The results of the therapeutic effect were separated into both short-term and long-term results. For the short-term effect, of the 52 cases in the treatment group: 27 cases scored remarkable effect, 19 cases were marked as effective and 6 cases ineffective for a total effective rate of 88.5%. In the control group, 16 cases reported a remarkable effect, 21 cases were observed as effective and 15 cases as ineffective for a total effective rate of 71.2%. After treatment, the remarkably effective rate and total effective rate in the acupuncture plus drug group were better than those in the control group ($P<0.05$).

In a survey regarding the long-term therapeutic effects of the treatments, 45 cases were re-evaluated from the acupuncture plus drug group six months to one year after

stopping treatment. 16 patients kept well with no recurrence found, 20 patients occasionally had a relapse of symptoms, but were improved compared to pre-treatment; and 9 patients reported a relapse of their symptoms to the same level as pre-treatment. This data showed a long-term effective rate at 80%. There was no significant difference compared with the therapeutic effect when the patients stopped treatment ($P>0.05$).

Table 2. Summary of Zheng, Yuan, and Zhang, 2004

Research Design	RCT
Participants	Sample size: 104 = 52 in treatment group, 52 in control group
Interventions	Acupuncture, EA, 2 ml Snow Lotus Injection; 20 total treatments Table 10 for acupoints
Comparison	Control group: 500 µg Mecobalamin
Outcomes	Total effective rate: 88.5% vs 71.2% in control group ($P<0.05$)

#3 RCT on DPN (Garrow, Xing, and Vere, 2014)

In a pilot RCT on the role of acupuncture in the management of DPN from the UK, 45 patients were randomly allocated to receive a 10-week course of either real or sham acupuncture. The outcomes were measured by the LANSS Pain Scale, the VAS, and the MYMOP (Appendix A). The MYMOP and VAS were completed after each treatment. The criteria for participation in the study were patients with a clinical diagnosis of DPN who were taking a prescribed drug for DPN and had not previously received acupuncture treatment. Of the 45 patients that completed a baseline and final assessment, 24 (53%) received active acupuncture while 21 (47%) were part of the sham acupuncture group. The results of the study concluded that there were small improvements in the VAS and MYMOP for the active acupuncture group with little change in the sham acupuncture

group. The LANSS Pain Scale did not produce significant results in either group that would indicate an improvement in symptom relief.

Table 3. Summary of Garrow, Zing, and Vere, 2014

Research Design	RCT
Participants	Sample size: 45 = 24 in treatment group, 21 in control group
Interventions	Acupuncture, 10 sessions, Table 10 for acupoints
Comparison	Control group: Park Sham Device
Outcomes	Small improvements in VAS & MYMOP vs no change in control group. No significant improvement on LANSS pain scale.

#4 Clinical Study on DPN (Bailey, Wingard, and Allison, 2016)

In a clinical study from the Southern California Tribal Health Center conducted between 2011 and 2013, 25 patients who reported DPN symptoms on their lower extremities during the previous 4 weeks were given acupuncture treatments once per week over a 10-week period. The results were based upon the NTSS-6, the NDS and LDF. These tests were used to determine the subjectivity of relief of specific symptoms of PN based upon a baseline score before and after the completion of the treatment period. 19 of the 25 subjects completed the treatments and all reported significant reduction in their PN symptoms of aching pain, burning pain, tingling/prickling sensation, numbness and allodynia/sensitivity to touch. Aching pain was the most commonly reported symptom that was relieved. Lancinating pain, which was shooting or electric in nature did not diminish significantly.

Table 4. Summary of Bailey, Wingard, and Allison, 2016

Research Design	Clinical Study
Participants	Sample size: 19 patients completed study
Interventions	Acupuncture, 10 total treatments, Table 10 for acupoints
Comparison	Control group: none
Outcomes	All participants reported significant reduction in aching, burning, tingling/prickling, and allodynia. No significant change in lancinating pain

#5 RCT on Chronic PN (Penza, Bricchi, and Scola, 2011)

A double-blind, placebo-controlled crossover study on the effects of EA on chronic painful neuropathy was published in 2011. The study contained 16 subjects of which 4 cases of PN were due to complications from diabetes, while the remaining 12 were of an idiopathic nature. The design of the study was to provide 6 sessions of EA for 30 minutes at intervals of 5-7 days for the treatment group. The control group was developed using a psuedo-EA technique of applying acupuncture needles to neutral anatomical points close to the traditional acupuncture points used in the treatment groups. At the end of the 6 sessions of EA and psuedo-EA, there was a pause of 12 weeks at which time the treatment and control groups were then switched. The primary outcome of the study was the number of patients treated with EA achieving at least 50% pain relief at the end of each treatment compared with pain intensity at baseline. The final results of the study indicated that only one patient per group achieved therapeutic effect after treatment compared with pain intensity at baseline.

Table 5. Summary of Penza, Bricchi, and Scola, 2011

Research Design	RCT, double-blind
Participants	Sample size: 16 patients; 12 idiopathic PN & 4 DPN
Interventions	EA, 6 total treatments then switched with control group after 12 weeks, Table 10 for acupoints
Comparison	Control group: Psuedo-Acupuncture
Outcomes	Only 1 patient in both treatment and control group achieved at least 50% pain relief. No significant changes concluded.

#6 RCT on CIPN (Han, Wang, and Shi, 2017)

In a RCT from China completed in 2017, researchers setup a study to determine if patients diagnosed with multiple myeloma (MM) who had incidences of peripheral neuropathy due to chemotherapy treatment could benefit from acupuncture. The design of the research study was to place the subjects into two groups. The treatment group was given a combination of both acupuncture and methylcobalamin, while the control group was provided with just the methylcobalamin. 500 µg of methylcobalamin was administered as an intramuscular injection every other day for 20 days followed by 2 months of oral administration of the same dose three times per day. These doses were provided to both the treatment and control group with the only differing factor between the groups being the acupuncture treatments. 104 patients met the inclusion criteria set forth by the researchers and were split evenly into the treatment and control groups. Evaluations for the results were contrasted with three different methods: VAS pain levels, quality of life and NCV. The NCV was tested via skin surface electrode tests of the MCV of the bilateral median and peroneal nerves as well as SCV of the bilateral median and the sural nerves. The results of the VAS pain score indicated that the patients in the

treatment group had a decrease in pain of 85.7% (42/49 patients) compared to 77.6% (38/49 patients) in the control group ($P < 0.01$). The quality of life scores, which were evaluated by FACT/GOG-NTx questionnaire, indicated significant improvement of nervous system symptoms in the treatment group ($P < 0.001$), but not in the control group ($P < 0.05$). The results for the NCV tests indicated that the treatment group showed improvement with the MCV and SCV ($P < 0.01$), but not the median nerve SCV, while the control group had no effect on SCVs or MCVs ($P < 0.05$).

Table 6. Summary of Han, Wang, and Shi, 2017

Research Design	RCT
Participants	Sample size: 104: 49 in treatment group, 49 in control group
Interventions	Acupuncture plus 500 µg methylcobalamin, 24 total treatments, Table 10 for acupoints
Comparison	Control group: 500 µg methylcobalamin
Outcomes	Significant improvement in VAS pain score, FACT/GOG-Ntx, MCV of bilateral median & peroneal nerve and no change in SCV of bilateral median nerve

#7 Single-Arm Study on CIPN (Garcia, Cohen, and Guo, 2014)

A study was published in 2014 on the effects of EA on patients with MM who were experiencing CIPN from intake of thalidomide and bortezomib. Of the 27 patients that met the eligibility criteria set forth by the researchers, 19 completed the study with 8 dropping out. No control was established for this study. The results were scored and analyzed using three subjective testing methods, the FACT/GOG-NTx, BPI-SF, and

FACT-G with measurements taken at four intervals: Baseline, 4 weeks, 9 weeks and 13 weeks. The results for FACT/GOG-NTx indicated that the mean scores improved significantly between baseline and each of the time intervals: 4 weeks ($p=0.0263$), 9 weeks ($p<0.0001$) and 13 weeks ($P<0.0001$). For the BPI-SF score, significant improvement was found at all intervals as well ($p<0.0001$). The FACT-G scores also revealed improvement on the physical well-being scale ($p=0.0004$) with improvement from baseline to the end of treatment at week 9 ($p<0.05$) and from baseline to follow-up at week 13 ($p=0.01$).

Table 7. Summary of Garcia, Cohen, and Guo, 2014

Research Design	Single-Arm Study
Participants	Sample size: 19 patients completed study
Interventions	EA, 20 total treatments, Table 10 for acupoints
Comparison	Control group: none
Outcomes	Significant improvement in FACT/GOG-Ntx, BPI-SF and FACT-G at all intervals of 4, 9 and 13 weeks. No improvements found in social/family, emotional or functional well-being

#8 Pilot study for CIPN (Bao, Goloubeva, and Pelsler, 2014)

In 2014, a study from The University of Maryland School of Medicine in the USA was published on CIPN specifically due to bortezomib on patients with MM. Eligibility criteria was set for patients who had been treated with bortezomib in the past with persistent CIPN grade \geq 2 (See Appendix B). Of 46 patients with MM that were screened, 27 patients met the eligibility criteria and enrolled. Of those 27, 2 withdrew after the first treatment and 4 withdrew after 4 weeks. Assessments were performed and analyzed both

objectively using nerve conduction studies and subjectively using the FACT/GOG-NTx and NPS questionnaires. Results were recorded at week 10, after the final treatment, and week 14, 4 weeks after the final treatment. Mean FACT/GOG-Ntx and NPS scores decreased from significantly at week 10 and 14 ($P < 0.0001$). Among the 25 patients who completed at least 4 acupuncture treatments, 14 (56%) reported improved daily functions; 10 (40%) reported greater than 50% decrease in average NPS, and 7 (28%) reported a greater than 50% reduction in FACT/GOG-NTx total scores. 18 (69%) had least a 30% reduction in NPS scores from baseline to the end of acupuncture treatments. No significant correlations were observed between symptoms/functional improvements and results in the nerve conduction studies.

Table 8. Summary of Bao, Goloubeva, and Pelsler, 2014

Research Design	Pilot Study
Participants	Sample size: 24 patients completed study
Interventions	Acupuncture, 12 total treatments, Table 10 for acupoints
Comparison	Control group: none
Outcomes	Significant improvement on FACT/GOG-Ntx & NPS tests; no significant change on nerve conduction studies

Table 9: Condition, Sample Size (n), Treatment Type, Control Group

Study	Condition	Size	Treatment Type	Control
Zhang et al.	DPN	65	Acupuncture	Inositol - 2g 3x/day
Zheng et al.	DPN	104	Acupuncture Electro-acupuncture 2ml Snow Lotus Injection	500 µg Mecobalamin
Garrow et al.	DPN	45	Acupuncture	Park Sham Device
Bailey et al.	DPN	19	Acupuncture	None
Penza et al.	DPN & Idiopathic	16	Electro-acupuncture	Pseudo-Acupuncture
Han et al.	CIPN	49	Acupuncture & 500 µg Methylcobalamin	500 µg Methylcobalamin
Garcia et al.	CIPN	19	Electro-acupuncture	None
Bao et al.	CIPN	24	Acupuncture	None

Table 10: Treatment Strategies

Study	Point Selection	Treatment Time	Frequency	Treatments per week
Zhang et al.	Main points: BL18, BL20, BL23, BL58, ST36, SP6, SP3, CV6, CV4, ST40, GB34 Auxiliary points: LI15, LI11, LI10, LI4, ST31, ST32, ST34, ST43, ST44, SP10, BL17, SP9, SP8, Bafeng & Baxie	25 minutes	14 daily sessions x5 Break: 5 days	5.4
Zheng et al.	Manual acu: T7Jiaj, BL23, CV6, CV4, GB30 EA: SP6 bilateral Injection: Bilateral T7Jiaji & SP6	30 minutes	10 sessions every other day x2	3.5
Garrow et al.	LR3, KI3, SP6, SP10 & ST36	30 minutes	10 sessions 1x/week	1
Bailey et al.	ST32, SP7, SP9, LR7, KI9, GB34, GB37, ST37, ST42, KI3, LR4, KI1, Bafeng	30 minutes	10 sessions 1x/week	1
Penza et al.	EA Group: ST36, SP6, LR3, BL60 Psuedo-EA: Neutral points near acupoints	30 minutes	6 sessions 1x/5-7 days EA & Psuedo-EA groups switch after 12 week pause	1
Han et al.	LR3, ST43, GB41, SP6, ST36, SP10, ST25, GV14, GV12, GV11, GV9, BL13, BL17, BL58	30 minutes	1 cycle = 1 session/day for 3 days, then 1x every other day for 10 days for 3 cycles	3.5
Garcia et al.	Manual Acu: SP6, ST36, Ba Xie 2 & 3, Ba Feng 2 & 3, Du20, CV4, CV6 EA: LI4 to SI3 LV3 to GB42 2-100 Hz for 20 minutes	20 minutes	9 weeks 2-3x/week	2.22

Bao et al.	LI4, TE5, LI11, ST40, Ba Feng Auricular: Shen Men, Point Zero plus 2 points where electro-dermal signal detected	20 minutes	2x/week for 4 weeks Biweekly for 4 weeks	1.25
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Table 11: Statistical Significance

Study	Statistical Significance
Zhang et al.	p<0.05 significant difference between treatment group & control group
Zheng et al.	p<0.05 significant difference between treatment group & control group
Garrow et al.	LANSS score: 95% CI = -1.1 to 5.2 VAS score: 95% CI = -4 to 19 MYMOP score: 95% CI = 0.3 to 1.4
Bailey et al.	NTSS-6 Scores: Aching Pain: p =0.035 Burning Pain: p = 0.008 Tingling/Prickling: p = 0.003 Allodynia: p = 0.029 Lancinating pain/NDS score/LDF: No significant change
Penza et al.	No significant change
Han et al.	VAS pain score: p<0.0001 significant improvement in treatment group compared to control group (p<0.01) FACT/GOG-Ntx: p<0.001 significant improvement in treatment group compared to control group (p>0.05) MCV of bilateral median nerve: p<0.05 significant improvement MCV of peroneal nerve: p<0.01 significant improvement SCV of bilateral median nerve: p >0.05 no change SCV of Sural nerve: p<0.01 significant improvement
Garcia et al.	FACT/GOG-Ntx at 13 weeks: p< 0.0001 significant improvement BPI-SF at 13 weeks: p<0.0001 significant improvement FACT-G at 13 weeks: p = 0.0004 significant main effect of time for physical well-being; no improvements in social/family, emotional or functional well-being
Bao et al.	FACT/GOG-Ntx: p<0.0001 significant decrease in pain and improved function NPS: p<0.0001 significant improvement Nerve conduction studies: no significant change

Retrospective Studies

#1 Retrospective Service Evaluation on CIPN (Donald, Tobin, and Stringer, 2011)

A study of 18 patients with PN due to chemotherapy related side-effects in northwest England was evaluated from January to August 2010. The design of the study was purely based upon evaluation without a control group. Once confirmed for suitability to receive acupuncture, the patients in the study were offered weekly treatments over the course of six weeks. The criteria for study was completed on an evaluation form with results categorized as improved, unchanged, aggravated, increased or other. Additional criteria recorded were based upon the quality of life improvements. These were relaxation, reduced stress, better sleep, improved mood, less medication and other. These forms were completed by the therapist prior to the first treatment and at the end of the sixth treatment. The results of the evaluation were finalized based upon 17 of the patients as one died during the course of treatment. Of the patients that completed the treatments, 82% reported that acupuncture improved their PN symptoms while 18% reported no change. There were no reports of deterioration from the treatments. 35% reported one additional benefit, 41% of the patients reported more than one additional benefit, and 25% reported no additional benefits from the treatments.

#2 Retrospective analysis on CIPN (Horin, Kahan, and Ryvo, 2017)

A retrospective study from the Tel Aviv Sourasky Medical Center in Tel Aviv, Israel gathered medical records from 28 breast cancer patients who had been concomitantly treated with various forms of chemotherapy between 2011 and 2012. The aim of the study was to determine if a combination of acupuncture and reflexology was effective for treating CIPN. The chemotherapy agents for the majority of the patients (54%) were doxorubicin and cyclophosphamide. The other agents taken by members of the study were adriamycin, capecitabine, carboplatin, docetaxel, paclitaxel, trastuzumab, and vinorelbine. Of the 28 patients screened, 71% presented with sensory neuropathy, 25% had motor neuropathy, 7% could not be classified and one patient had both motor and sensory neuropathy. Neuropathy severity was graded using the NCI-CTC 4.0 and assessed at regular intervals every three months. On average, the acupuncture protocol was administered 105 days after initiation of each course of chemotherapy. The results found that out of 16 of 21 patients who presented with grades 1 to 2 neuropathy and all 7 patients with grades 3 to 4, 23 (82%) patients in total were symptom-free 6 months after starting their acupuncture protocol and 26 (93%) experienced complete resolution of symptoms at the 12-month follow-up. No adverse effects were observed in any of the patients.

IV. DISCUSSION

Of the eight main studies summarized in Tables 9, 10 and 11, positive evidence for the efficacy of acupuncture in treating PN was found in seven out of eight cases; however, there are limitations in confirming that evidence with certainty. Standardized protocols for treatment and control in studies involving acupuncture for PN has not been established; therefore each of the studies used different criteria in attempting to analyze therapeutic efficacy. Evaluation methods were differentiated with mixed testing methods focusing on both objective and/or subjective results. The FACT/GOG-Ntx assessment was a standard method of evaluation used commonly between the studies focused on CIPN. The different criteria within each study deviates from each other in regards to type of acupuncture (manual acupuncture or EA), method of control, acupuncture points selected, total number of treatments and the frequency in which the treatments occurred.

Control Groups

There is no standard for control in RCTs on acupuncture at this time, therefore each study had their own method in place to establish the independence of the acupuncture groups. Out of the eight studies explored in detail, three included a supplemental method for control, two studies utilized a sham-acupuncture method and three studies established no basis for control.

Supplemental Control

Two of the studies, Zheng et al. (2004) and Han et al. (2017), based upon different causes of PN, DPN and CIPN respectively, utilized similar supplemental control through the use of the cobalamin derivatives, mecobalamin and methylcobalamin. Cobalamin, commonly referred to as vitamin B12, has been shown to improve nerve conduction velocity and promote regeneration of injured nerves (Zhang, Han, Hu, 2013). These studies were designed to test acupuncture's effectiveness by using combination therapy of both the acupuncture and mecobalamin or methylcobalamin and then comparing the results with a control group consisting of solely the mecobalamin or methylcobalamin. Both studies resulted in positive findings for the acupuncture treatment groups as more effective compared to the control group alone, which suggests that acupuncture may be effective for either type of PN regardless of its etiology. The third study to use a supplement for the control group, Zheng et al. (2004), gave their non-therapeutic group oral doses of inositol, but not in combination with acupuncture. While the acupuncture group did find a significant difference in clinical efficacy between the two groups, the resulting correlation for positive therapeutic effect regarding acupuncture treatment could have been improved if the study established a stronger control group designed with combination therapy.

Sham Acupuncture

Sham acupuncture has become a common method for control in studies attempting to determine the efficacy of acupuncture, but there is not a standard protocol in place on how it is performed (Zhang, Chu, and Wang, 2016). The idea behind it is to create a condition in which the patient is unaware that they are receiving an acupuncture treatment or a placebo treatment, either by simulating the feeling of acupuncture or by placing the needles in a neutral site. The two studies to include a sham control group, Garrow et al. (2014) and Penza et al. (2011), are examples of these two different types of methods; the former using a Park Sham Device and the latter placing the needles away from the correct acupuncture points. The results of Garrow et al. concluded that improvements in 25% of the VAS pain intensity score favored the active group compared to the sham group by 33.5%, but improvements were found in both groups. To account for the psychological factor of possible placebo, they asked the participants three months after the final treatment if they thought they had received the active or sham treatment. 40% of participants in the active group believed they had received sham acupuncture and 42% in the sham group believed they had received a real treatment. These similar results correlate to non-biased owing to the blinding effects. Penza et al. did not find a difference between the EA and pseudo-EA groups with only one participant achieving positive results in each group.

Point Selection, Pattern Diagnosis, Frequency and Treatment Amounts

The rationale for why all of the specific points were chosen in each study was determined by the experienced practitioners in charge of each actual treatment. While all studies included traditional acupuncture points, deviations in point selection were found in every study. The most commonly used points were SP6 and ST36, used in five out of the eight studies. The next most common point used in four of the studies was Bafeng. Finally, CV4, CV6, LI4, LR3, SP10 and BaXie, were all found to be used concomitantly across three studies. The variations in point selections represent one of the issues with research methodology for acupuncture, seeing as positive results can be possibly achieved using different protocols. Taking into account the location of patient's PN symptoms is also a reason for point selection deviation as shown in Zhang et al. (2010) and Bailey et al. (2016), which used a myriad of traditional points on the limbs located proximally to common areas of affected nerves.

Pattern diagnosis was not discussed in the studies, as the necessity for the same point protocol across the treatments within a single study had to be maintained rather than choosing based upon each patient's individual diagnosis. However, when looking at the common points and meridians used in each protocol, the diagnosis of the root of PN symptoms is attributed to deficiencies, therefore the protocols used more points on the yin channels when treating distally.

Correlation between positive effect and the number and frequency of treatments, as well as amount of points selected, cannot be determined due to the lack of standardization across all of the studies; however, it can be noted that the one study that did not meet the

criteria for positive results, Penza et al., (2011), analyzed the lowest number of treatments, with the fewest amount of patients, and selected the fewest number of points. The median average number of treatments performed across all 8 studies was 14.5 and median average frequency was 1.74 treatments per week. Future studies should be established to determine if frequency and amount of treatments is an important factor in determining acupuncture's overall effectiveness.

Safety and Risk

Safety and risk of acupuncture treatments are one of the strongest factors in exploring its proposed use for treating PN. Among all studies examined in this review, there were no incidences of serious adverse reactions and no serious complications were observed even when the treatments were found to be ineffective. In a prospective survey of 34,407 treatments from York, UK, there were no reports of serious adverse events, defined as events requiring hospital admission, leading to permanent disability, or resulting in death (95% confidence interval 0 to 1.1 per 10,000 treatments). Practitioners did, however, report 43 minor adverse events, a rate of 1.3 (0.9 to 1.7) per 1,000 treatments (MacPherson, Thomas, and Walters, 2001). Given this positive safety record and low risk, larger scale studies on acupuncture are warranted in the future.

Criteria of Effectiveness

The criteria of effectiveness used to determine if acupuncture is a viable treatment method has many variable components that was not uniform across any of the studies.

This variation can be split by disseminating the results based upon either specific objective measurements of quantifiable improvement or tests aimed at determining the patients' opinions on how they subjectively feel. Common tests to determine objective results used among the studies were motor and nerve conduction velocity tests aimed at testing whether measurable improvement could be found in nerve function. In the studies that utilized these methods, positive results were mixed with moderate improvement found in some and no significant change in others.

The mutual test used to determine subjectivity of improvement in patients with CIPN was the FACT/GOG-Ntx questionnaire. This questionnaire asks patients how they feel based upon the criteria of physical, social/family, and functional well-being, as well as additional concerns regarding their physical symptoms. All three studies that utilized this test found significant improvement in subjectivity of improvement of patients' symptoms. Further research should be conducted using these standard tests as they are viable methods of measurability that can provide positive results in determining how acupuncture can improve patients with PN.

Author's Opinion

Based upon the results found within this review, the limitations found in the research of studies on acupuncture poses a great problem with integrating the practice into the evidence-based research model. Examples have been found in which there is overwhelmingly positive results of both objective and subjective measurements of improvement in the quality of life of those suffering from PN; however, these results

cannot be used as a determining factor to definitively state that acupuncture is effective because of the presented limitations. Current pharmaceutical treatment methods themselves seem limited in that their criteria for use is only that they work better than placebo and have an effective rate of around 30 to 50%, yet they are the first line of treatment in the United States and riddled with side-effects. Among the studies discussed in this review, only one study was conducted in the United States, and was based solely upon a very specific subset of the population. This lack of research can be traced to the controlling influences of research in the United States and over-ride the necessity for rigorous scientific study in a field that has a potential for great results.

Acupuncture as a practice is growing in popularity because from an individual perspective, the treatments do work at least on an anecdotal basis. The best chance for it to integrate and proliferate into the western healthcare system is through proper understanding of the scientific mechanism of how acupuncture affects the nervous system and how this mechanism can initiate a healing response. With this understanding, new scientific standards for effectiveness can be developed and studied in a way that fits into the eastern perspective on medicine.

V. CONCLUSION

Current methods for helping the exponentially increasing population suffering from PN are limited and wrought with adverse effects necessitating a low-risk, safe alternative treatment source. Acupuncture fits this criteria as a time-tested modality with a unique ability to help individuals by re-signaling their nervous system to reduce their subjective feelings of pain, while simultaneously providing an internal environment of activation of the body's natural healing mechanisms to treat the cause of disease. Because of the limitations presented in this review that are inherently found in acupuncture research, understanding these mechanisms is an important factor in helping to integrate the practice into the evidence-based research system and can be used to help develop future techniques in order to achieve more accurate and unbiased scientific results.

Despite the positive results in the majority of the studies found in this review, the effectiveness of acupuncture for the treatment of CIPN or DPN cannot be determined due to lack of standardization, small sample sizes, and poor control methods. Future, large-scale, uniform research is warranted because positive results from acupuncture treatment has been found to have the potential to improve the quality of life in individuals suffering from PN.

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VII. APPENDICES

Appendix A: Assessment Tests

BPI-SF: Brief Pain Inventory-Short Form

FACT/GOG-NTx: Functional Assessment of Cancer Therapy/Gynecological Oncology

Group-Neurotoxicity scale

FACT-G: Functional Assessment of Cancer Therapy-General

LDF; Laser Doppler Fluxmetry

LANSS: Leeds Assessment of Neuropathic Symptoms and Signs

MCV: Motor Conduction Velocities

MYMOP: Measure Yourself Medical Outcome Profile

NCV: Nerve Conduction Velocity

NDS: Neuropathy Disability Score

NTSS-6: Neuropathy Total Symptom Scale

NPS: Neuropathy Pain Scale

SCV: Sensory-nerve Conduction Velocities

VAS: Visual Analogue Scale

Appendix B: Grades of CIPN According to NCI-CTC 4.0

Grade I: Paresthesia or areflexia without pain or loss of function

Grade II: Symptomatic, interferes with function but not daily living activities

Grade III: Symptomatic, interferes with daily living activities

Grade IV: Sensorimotor neuropathy that significantly interferes with daily living activities