# Acupuncture is “Reasonable and Necessary” for Peripheral Neuropathy

## A formal request to the Centers for Medicare and Medicaid Services for a National Coverage Determination submitted by the Acupuncture Now Foundation

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## Acupuncture is “reasonable and necessary” for the treatment of peripheral neuropathy

## Plain Language Summary

1. Peripheral neuropathy (PN) has a large and increasing disease burden in the USA, especially in older adults.

2. Distal Sensory Polyneuropathy, also referred to as “stocking and glove PN”, is a common condition in diabetics, those undergoing chemotherapy, HIV/AIDS patients, and those of unknown origin (idiopathic).

3. Current medications target pain with limited success but do not address PN symptoms such as numbness and paraesthesia. Some of these medications (such as opioid analgesics) also have problematic benefit to harm ratios.

4. Over the last two decades, dozens of studies on acupuncture and electroacupuncture have found that those therapies are effective not only in alleviating PN pain, but also in improving numbness and paraesthesia.

5. Many acupuncture PN studies also found improvements in objective nerve conduction studies in addition to the subjective symptom improvements.

6. Improved nerve conduction studies strongly suggest that acupuncture may trigger regeneration of peripheral nerves that are damaged in PN.

7. Additional mechanism studies suggest that acupuncture’s ability to stimulate regrowth of damaged peripheral nerves may be due to improved vascular microcirculation while more recent studies have found regrowth appears to be mediated by increases in neurotrophins, especially BDNF (brain-derived neurotrophic factor).

8. Although a majority of the PN studies on acupuncture and electroacupuncture to date have been limited by small sample sizes and suboptimal protocols and reporting, there is sufficient evidence to confirm that acupuncture and electroacupuncture can safely improve numbness and

paraesthesia as well as pain, measured by both symptomatic improvements and nerve conduction studies.

9. Considering the size of the disease burden (and increasing economic costs) of PN and the lack of safe and effective treatments for non-pain symptoms included within current standard care, the inclusion of acupuncture and electroacupuncture in standard care for older adults suffering from PN would alleviate much suffering and increase quality of life.

10. Given the balance of evidence regarding acupuncture's benefit to harm ratio in treating PN, acupuncture should be regarded as "reasonable and necessary" for Medicare beneficiaries. As such, the Centers for Medicare & Medicaid Services should authorize coverage for acupuncture for peripheral neuropathy under section 1862(a)(1)(A) of the Social Security Act.

**Table of Contents**

# A Complete, Formal Request for a National Coverage Determination:

### Acupuncture is "reasonable and necessary" for the treatment of peripheral neuropathy

**Submitted electronically February 7, 2024**

## Introduction

The Acupuncture Now Foundation, a U.S. based, educational, for the public benefit 501(c) (3) (non-profit) organization, formally requests that the Centers for Medicare and Medicaid Services (CMS) undertake a National Coverage Determination (NCD) for acupuncture services in the treatment of peripheral neuropathy.

It is estimated that at least 20 million Americans have some form of peripheral neuropathy (PN) although that number might be much higher.[1] Distal Sensory Polyneuropathy (DSP), often referred to as "stocking and glove" PN, is the most common of the more than 100 types of PN. DSP/PN (hereafter referred to as "PN")* is a common and serious complication for diabetics, those undergoing chemotherapy, and people with HIV/AIDS. About 1/3 of these PN cases are of unknown origin (idiopathic).[2]

The suffering this type of PN causes can go far beyond the pain and quality of life problems that are most commonly associated with this condition. In diabetics, numbness in the lower extremities is the leading cause of foot sores. Those sores can lead to amputation with about 50% of the annual 86,000 foot amputations in the U.S. happening to diabetics.[3] DSP also causes balance and gait problems and increases the risk of falls.[4]

Chemotherapy induced peripheral neuropathy (CIPN) is commonly referred to as a "dose limiting" side-effect of neurotoxic chemotherapy because the PN symptoms can be so severe that the dosage of chemotherapy is often reduced or even suspended to try to ease those symptoms. Lowering the dosage of chemotherapy can reduce the cancer fighting ability of that therapy and places cancer patients at greater risk.

A few medications have shown limited success in treating the pain associated with PN. Although not recommended as a front-line treatment in chronic cases, opioids are likely still the most commonly prescribed medication for the pain associated with this condition.[5]

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Footnote:

*Although all types of DSP are a type of PN, not all types of PN involve the multiple distal sensory nerves the term DSP designates.

However, there currently are no effective medications for the numbness and range of troublesome sensations that plague PN sufferers due to what has long been considered irreversible nerve damage especially to sensory nerves. To illustrate the range of non-pain symptoms which PN sufferers experience, the following list of patient reported outcome measures (PROMs) were used as outcome measures in a recent CIPN study[6]: neuropathic pain, hyperesthesia, feeling of cold, feeling of heat, burning pain, tingling, cramps, numbness, unsteadiness of gait, negative impact on daily activities, negative impact on sleep quality, frequency of symptoms.

Over the last two decades, there has been a growing body of evidence regarding acupuncture's ability to treat not just the pain but also the numbness and the many other symptoms associated with PN. As will be detailed, the evidence strongly suggests that acupuncture has the potential to induce nerve regeneration, or at least measurably improve nerve functioning. This represents a significant advancement in the management of the most common types of PN. Any therapy shown to be able to cause such functional nerve improvement for these patients in a safe manner should be regarded as a front-line treatment for this condition.

Considering that a majority of PN sufferers, especially those of the diabetic and idiopathic types, are older adults of Medicare age, the evidence warrants the Centers for Medicare and Medicaid Services to undertake a National Coverage Determination and ultimately approve the coverage of acupuncture to treat PN related conditions under section 1862(a)(1)(A) of the Social Security Act. Note that acupuncture falls within one of the statutorily defined benefit categories outlined in the Social Security Act, qualifying as:

Incident to a physician's professional service (§ 1861(s) (2) (A))

Inpatient Hospital Services (§ 1861(b))

Outpatient Hospital Services Incident to a Physician's Service (§ 1861(s) (2)(B))

Physicians' Services (§ 1861(s) (1))

The case for approving coverage for acupuncture will be made by detailing the evidence including highlighting several published systematic reviews (SRs) and meta-analyses (MAs) of randomized controlled trials (RCTs) and individual RCTs, the vast majority of these finding positive outcomes. We will also summarize relevant mechanism studies. As part of this NCD request, we are also electronically sending copies of some 72 full studies.

At present, acupuncture services have only been approved for Medicare coverage by the CMS for one condition; chronic low back pain.

In the January, 21 2020 National Coverage Analysis Decision Memo CAG-00452N "Acupuncture for Chronic Low Back Pain", the CMS notes how their reviewers found the balance of evidence supported the use of acupuncture for that condition and then approved its coverage.

Virtually all the considerations detailed in that Chronic Low Back Pain Decision Memo also apply to this NCD request: how "Medicare recognizes the importance of having treatment options to allow an integrated approach that is tailored to the needs and preferences of Medicare patients", that the "decision regarding coverage takes into account an assessment of benefits and harms and the opioid public health crisis", and how, owing to acupuncture's well known safety profile, your review found "serious adverse events were rare with acupuncture and control interventions".

Those considerations led CMS to conclude "We believe that in light of the relative safety of the procedure and the grave consequences of the opioid crisis in the United States, there is sufficient rationale to provide this nonpharmacologic treatment to appropriate beneficiaries with chronic low back pain."

In the case of PN, the evidence is even more compelling due to the combination of acupuncture's ability to provide safe, drug free pain relief together with its potential to provide relief for the serious non-pain complications this condition causes.

However, an important aspect of the evidence presented here is how to put the details of the published acupuncture studies into perspective. There has long been a tendency in acupuncture research conducted in the West to underestimate acupuncture's specific effects (efficacy) while overestimating its non-specific effects, which are often described as placebo effects.

The reason for this is twofold: First, the acupuncture profession has yet to develop best-practice clinical guidelines for the various medical conditions acupuncturists treat. This being the case, acupuncture researchers have no industry-vetted guidelines to help them develop the clinical protocols they should employ when trying to determine acupuncture's efficacy for any given condition. The absence of such guidelines has led to widely varied and often sub-optimal clinical protocols being employed in many acupuncture research trials especially those conducted in the West. This, in turn, has led to a higher risk of false negative outcomes.[7]

Second, the well-intended desire to employ a placebo control in acupuncture research has proven nearly impossible to successfully carry out. Failings in early attempts to develop inactive (placebo) controls spurred the development of no fewer than six different types of acupuncture placebo controls that compromise the validity of the research these controls are employed in. A study which examined the three most commonly used sham/placebo needle devices, the Streitberger, Park and Takakura sham/placebo needle devices; found that none of these devices are, in fact, inert.[8]

This combination of no clinical guidelines to aid researchers in employing effective clinical protocols and the inability to establish a truly inactive placebo control has led to a great deal of mixed results (heterogeneity) in acupuncture research especially in systematic reviews. Skeptics of acupuncture's legitimacy point to these mixed results as proof that the positive clinical effects seen in the vast majority of studies undertaken on acupuncture are due to the placebo effect.

Such criticisms not only ignore the fact that there are no clinical guidelines or valid inactive placebo controls being employed in acupuncture research, but they also ignore the excellent benefit-to-harm

ratios consistently seen in acupuncture research. If acupuncture did not routinely produce positive effects, there would be no need to debate what percentage of those effects was happening via the placebo effect.

While the two factors mentioned above has led to a tendency to underestimate acupuncture's efficacy, fortunately, in the case of treating the conditions associated with PN, the last ten years have begun to see an emerging consensus within published research around the critical issues of acupuncture point selection and treatment frequency (dosage). These findings make it possible to identify the studies using better clinical protocols from those using suboptimal ones. As we will show, when you omit studies using suboptimal clinical protocols you find less heterogeneity in clinical effectiveness and clearer findings of positive effects. When you then devalue or altogether ignore the flawed placebo controls that continue to be employed in so many acupuncture studies, you can draw firmer conclusions about acupuncture's benefit-to-harm ratio.

# Presenting the Evidence Part One
## Idiopathic Peripheral Neuropathy

There have been far more studies published for methods of treating diabetic and chemotherapy-induced PN than for idiopathic or HIV/AIDS PN. The same applies for studies investigating acupuncture. However, we wanted to start our presentation of the evidence with a particularly important pilot study that investigated acupuncture in treating idiopathic PN.

Schröder S, Liepert J, Remppis A, Greten JH. Acupuncture treatment improves nerve conduction in peripheral neuropathy. *European Journal of Neurology.* 2007;14(3):276-281.[9]

This idiopathic PN pilot study was one of the first studies, if not the first, to employ before and after nerve conduction studies (NCS) to test what impact acupuncture might have on objective measures of both sensory and motor nerve function. The study's authors detail that in PN sufferers, nerve damage can occur to axon or myelin nerve cells and how NCS can measure this:

"*NCS can provide information as to the type of fibers involved (motor, sensory, or both), the pathophysiology (axonal loss versus demyelination) and the location of the nerve damage (symmetric versus asymmetric or multifocal pattern). Axon loss results in loss of amplitude of nerve action potentials, and myelin loss mainly results in slowed conduction velocities and prolonged distal latencies. It is therefore generally accepted that NCS is a most useful diagnostic tool in the evaluation of the type and course of PN."*

Their study titled "Acupuncture treatment improves nerve conduction in peripheral neuropathy" involved 21 patients (mean age 73, 9 males, 12 females)who were treated with acupuncture for PN of the lower extremities. The control group consisted of 26 patients (mean age 67, 13 males, 13 females) who received the best medical care but no specific therapy for PN. All subjects were carefully screened, and neurological exams and NCS testing confirmed their PN.

A significant change in nerve conduction of the sural or tibial nerve was defined as being 2 m/s slower or faster than the initial measurement. A change in the amplitude of sensory nerve action potential of more than 2 µV was defined as a significant aggravation or amelioration in the sural nerve. A change in the amplitude of the motor nerve action potentials of more than 2 mV was defined as a significant aggravation or amelioration in the tibial nerve.

Subjective parameters were evaluated by self-assessment on a three-point scale with patients being routinely asked if their symptoms of paresis (muscle weakness due to nerve damage), neuropathic pain or numbness (hypesthesia) were better, equal or aggravated after ten weeks.

The acupuncture group received ten once weekly treatments. While each acupuncture group patient underwent an individual diagnosis following Traditional Chinese Medicine (TCM) rationale, this study listed the most commonly used points as being what is referred to as "local" acupuncture points - those on the lower legs and feet. In addition to "local" acupuncture points, the use of "distal" acupuncture

points (a distance away from symptomatic body parts) is also commonly used in acupuncture therapy and deciding which class of points will be most relied upon is an important clinical consideration for acupuncturists .

Relying mostly on lower extremity acupuncture points (local points) for treating PN in the lower extremities is another important aspect of this study. It is an early example of a clear trend that is found in subsequent studies investigating what acupuncture points were most commonly used in acupuncture PN research. These studies found a good deal of overlap in the use of local points that were reported in successful outcome trials. We will detail some of these studies investigating the most commonly used acupuncture points in PN research in subsequent sections of this NCD submission.

While this pilot study involved a small number test subjects and did not involve a blinded control, it found several important results that helped to establish key aspects of treating PN in general and the use of acupuncture in particular.

They found, for example, that in both treatment groups the number of patients that suffered numbness outnumbered those who suffered from neuropathic pain, thus underscoring that effective treatment for PN is as much about treating numbness as it is about treating pain. Many studies on PN focus primarily, if not exclusively, on pain. And, while both the pain and numbness involved with PN are almost certainly due to nerve damage, it is possible to reduce pain without improving the underlying nerve damage. However, there is less likelihood of improving PN numbness without at least starting to improve the factors behind nerve damage.

And this is another important insight this study found. 7 of the 21 patients (33%) in the acupuncture treatment group reported immediate relief of subjective symptoms after the first 1-2 treatments. However, when they underwent nerve conduction testing at that time, none showed improvements in their NCS. At the end of the ten-week treatment period, when all test subjects underwent nerve conduction tests, it was then found that the 7 subjects who reported early improvement in subjective symptoms continued to report symptom improvements, but they now also exhibited measurable, objective improvements in nerve conduction.

This finding helps to underscore that subjective improvement may not indicate nerve improvement. It also strongly suggests that it takes several weeks - 10 or more - before the nerve regeneration made possible by acupuncture has a chance to take hold. Whether in clinical practice or in research studies, if one stops acupuncture therapy too soon, even with patients that are reporting subjective symptom improvement, such improvements are likely to be temporary. This would be akin to the temporary action of pain modulating drugs more so than the longer lasting improvement that would occur if some degree of neuroregeneration can be made to take place. More acupuncture treatments over longer periods of time have a better chance of producing higher success rates with longer-lasting benefits.

In total, 76% of the acupuncture-treated patients (16 of 21) reported an improvement after ten treatments including 50% (2 of 4) patients with motor palsies. 24% (5) reported no change. In the control group, 15% of the patients (4 of 26) reported an improvement of their symptoms, 46% (12) reported no change, and 36% (10) reported an aggravation.

At the end of 10 weeks, all of the 16 acupuncture-treated patients with subjective symptomatic improvement also had significant improvement of nerve conduction velocities or amplitude of sural or tibial nerve meaning there was a 100% correlation of NCS improvement with the reported subjective improvement. None in this group reported an aggravation of their symptoms. Of five patients whose symptoms did not change under acupuncture treatment, three had an aggravation of NCS findings and two did not show any change in NCS findings.

In the control group, 15% (4) patients reported an improvement of symptoms, which was paralleled by an amelioration of nerve conduction velocities, resulting in a 100% correlation between subjective assessment and objective assessment just as in the acupuncture group. 38% (10) patients reported an aggravation of symptoms, which was paralleled by an aggravation of nerve conduction velocities. Out of the 46% (12) patients without any change in symptoms, 19% (5) showed an aggravation and 27% (7) no change of NCS. Altogether 58% (15 of 26) patients of the control group showed an aggravation of nerve conduction velocities.

A detailed breakdown of the NCS testing results is given, including results at 4-month follow-up that found highly significant differences between the two groups for sural nerve amplitudes.

The following quotes from "Discussion" section of this study (minus the references) are presented below. These provide well-reasoned theories for the mechanisms behind acupuncture's ability to improve nerve function in PN suffers as verified by the nerve testing improvements seen in this study and based on previous findings of acupuncture animal mechanisms studies.

*"Our study shows that acupuncture treatment of PN results in a significant improvement of NCS of the sural nerve when compared with the control group. NCS data of the tibial nerve showed only partial improvement of the amplitude, because of small subgroups with motor involvement (acupuncture-group n = 14, control-group n =10). Even more importantly the improvement of NCS was fully correlated with a subjective improvement of symptoms. Therefore, this pilot study clearly demonstrates for the first time that not only subjective criteria, which are known to be biased by placebo effects but also objective criteria of NCS are positively correlated with the therapeutic intervention of acupuncture. Moreover, it is generally accepted that compromised nerve conduction in PN mainly depends on structural alterations of myelin sheaths, while the amplitude is correlated with the number of functional axons. Consequently, one may speculate that repeated therapeutic interventions by acupuncture over 10 weeks indeed not only improve the symptomatic state in PN but also induce a normalization of histological morphology. Further studies will thus have to include biopsy-analyses to prove this hypothesis.*

*In a subset of seven patients there was immediate symptomatic relief after one to two treatments. There was no change of NCS at this point, but improved NCS measurements were found after the full treatment period of 10 weeks. This may reflect that not only morphological alterations in the anatomy of peripheral nerves but also complex derangements in the regulation of pain threshold are of importance in the pathophysiology of PN. In this context, it has been hypothesized that either central nervous effects or peripheral mechanisms contribute to the early effect of acupuncture. One hypothesis relates to the enhancement of conduction by the dorsal column or higher centers. Peripheral mechanisms possibly*

*involved may include other types of fibres, such as the small unmyelinated or thin myelinated fibres, commonly believed to be undetected by NCS.*

*According to a modern understanding of acupuncture mechanisms, acupuncture may elicit vegetative reflexes, thereby changing the flow of blood and enhancing functional properties of connective tissue and organs. Litscher et al. have shown that acupuncture may increase blood flow in the limbs. Increased blood flow to the vasa nervorum and dependent capillary beds supplying the neurons may therefore contribute to the immediate effect of acupuncture. Over some time, these may contribute to nerve repair with measurable improvement of axons or myelin sheaths after 10 treatments. Local and central effects on vascularization may thus represent combined causes for regeneration."*

In closing, the authors of this study stated that the success of this pilot study justified the need to carry out a fuller RCT to further investigate their findings. There have been dozens of RCTs on acupuncture for PN carried out since the publication of this pilot study, the vast majority showing positive results. We will detail some of those as we divide the evidence into sections on diabetic and chemotherapy induced PN and a short review of HIV PN studies. We will also detail why the few negative outcome studies failed to show successful outcomes.

As we present evidence on acupuncture for DIPN and CIPN, we will first highlight studies that were carried out by some of the same researchers as in the group that did this idiopathic PN pilot study. We feel this approach is helpful because, to the best of our knowledge, the combination of these studies constitutes the most comprehensive and well-reasoned body of research that sets out with the goal of attempting to address weaknesses in previous acupuncture for PN research.

# Presenting the Evidence Part Two
## Diabetic Induced Peripheral Neuropathy (DIPN)

According to the CDC's latest National Diabetes Statistics Report, nearly 30% (16.5 million) of Americans over 65 years of age have diabetes. Further estimates are that 50% of diabetics 65 and over have diabetic-induced peripheral neuropathy (DIPN/DPN) that mainly involves distal sensory nerves (DSP)[10]. As the diabetic epidemic continues to grow so too do the numbers of those who develop DIPN.

While limited anticonvulsive and antidepressant drugs have been shown to have a modest effect over placebo in treating DIPN pain (referred to as diabetic peripheral neuropathic pain DPNP), it is widely believed that, as with the other primary types of PN, there is no accepted treatment to measurably improve the nerve cell damage that takes place with DIPN. This nerve cell damage is believed to be responsible for not just the pain but the range of other symptoms including loss of sensation and fine motor skill function that is so common in the major types of PN.

Here, we review a study by some of the same researchers involved in the pilot study on idiopathic PN we just considered:

Meyer-Hamme G, Friedemann T, Greten J, Gerloff C, Schroeder S. Electrophysiologically verified effects of acupuncture on diabetic peripheral neuropathy in type 2 diabetes: The randomized, partially double-blinded, controlled ACUDIN trial. *Journal of Diabetes.* 2021;13(6):469-481.[11]

This study rates as one of the best methodological quality studies on acupuncture in treating PN in general and DIPN specifically. The authors did an excellent job addressing the types of issues that have tended to lower the methodological quality of many acupuncture studies. For example, many acupuncture studies on PN utilize relatively small sample sizes mostly due to funding difficulties. In this study, the rationale for their calculations of needing 54 subjects in each of the three arms is given including figuring a 10% dropout rate thus settling on 60 subjects in each arm.

While many studies undertaken in China are funded by differing branches of Chinese government-funded healthcare institutions and the details of these funding sources are often not fully described, this study was funded by a large private German medical insurance company and clearly stated. Inclusion and exclusion criteria were also clearly stated, as were the details of blinding and randomization.

All the subjects had *"symptomatic symmetrical length-dependent sensorimotor DPN (DIPN) at the lower extremities, and showed abnormal results in NCS, sural sensory nerve action potential (SNAP) <10 μV, sural sensory nerve conduction velocity (SNCV) <42 m/s, tibial motor nerve conduction velocity (MNCV) <40 m/s, and tibial motor nerve action potential (MNAP) <8 mV)."*

The average age of subjects was 70 for the needle acupuncture and placebo arms and 72 for the laser arm, similar to the subject ages in the idiopathic study. Those ages are well within the Medicare age demographic of importance to CMS reviewers.

Perhaps most importantly, this study went to great lengths to try to provide a legitimate placebo/sham control arm. There is no accepted method for employing a true inactive placebo control for needle acupuncture. In this study, in addition to classical needle acupuncture, it was decided to employ a laser acupuncture active/verum arm and then a placebo laser control arm. How laser acupuncture could be controlled to provide a double-blinded and truly inactive control is well described in this study. In the words of the study's authors:

"*The definition of adequate control interventions for a double-blind study design has, despite many efforts, remained a methodological challenge in acupuncture trials. Sham needling performed away from acupuncture points or shallow needling elicits unspecific physiological responses on skin penetration and cannot be regarded as an inactive placebo intervention. To date, there are no international standards regarding direct placebo procedures for the evaluation of acupuncture effects in a double-blind study.*

*Therefore, we chose an indirect control for the ACUDIN trial, using laser acupuncture as a second treatment intervention. Laser needle is a particular type of laser acupuncture that has previously been shown to be equally effective as needle acupuncture and is suitable for placebo treatment, preventing any nonspecific physiological activation by deactivated laser irradiation. This can be completely concealed from the patient. Laser acupuncture has been previously evaluated as a valid control for classifying the effect of acupuncture needling.*

*Therefore, we included laser acupuncture as a second verum treatment and placebo intervention in a double blind procedure in the ACUDIN trial. Particulars are detailed in the previously published trial protocol."*

In short, this is good example of an acupuncture study that both followed good quality controls in the methodology of study design and implementation and also utilized adequate quality clinical protocols.

As with the 2007 idiopathic PN study, subjects in each study arm of this study were given ten once weekly treatments using local acupuncture points – these being at the base and the tips of each toe as well as a point just superior and lateral to the patella.

Neurological assessments, including nerve conduction studies (NCS) of sural and tibial nerves, were performed at baseline and weeks 6 and 15. The primary outcome was the delta of the sural sensory nerve action potential (SNAP). Secondary outcomes included further NCS values, clinical scores, and patient-reported outcome measures (PROMs).

*"Results: Of 180 participants, 172 completed the study. Sural SNAP and sural and tibial nerve conduction velocities improved significantly after 10 treatments when comparing needle acupuncture to placebo. Needle acupuncture showed earlier onset of action than laser acupuncture. PROMs showed larger improvements following needle and laser acupuncture than placebo, reaching significant differences for hyperesthesia and cramps following needle acupuncture and for heat sensation following laser acupuncture."*

*"Conclusions: Classical needle acupuncture had significant effects on DPN. Improvement in NCS values presumably indicates structural neuroregeneration following acupuncture."*

The following quote from the "Discussion" section of this study offers important insights regarding acupuncture's ability to facilitate nerve regeneration of sensory nerves including detailing animal mechanism studies. It also highlights that, as was found in the pilot study on idiopathic PN, DIPN primarily affects sensory nerves more than motor nerves thus making both types of PN primarily forms of distal sensory polyneuropathy.

"*Over a 15-week period, needle acupuncture induced significant improvement in the primary outcome variable sural SNAP and sural SNCV and tibial MNCV compared with placebo. Laser acupuncture induced improvement in both sural SNAP and SNCV compared with the baseline; however, it showed a later onset of effect compared with needle acupuncture and did not reach significance compared with placebo on completion of the study. Study design and power calculation were generated for needle acupuncture based on a prior case study. Laser acupuncture was implemented for the purpose of a double-blind comparison. Based on other publications, laser acupuncture was expected to yield equivalent effects to needle acupuncture. However, the results remained below those of needle acupuncture.*

*DPN affects primarily sensory rather than motor nerves. This was confirmed by fewer impaired baseline values and minimal, insignificant changes of tibial MNAP in all groups. Following needle acupuncture significant improvements could, compared with placebo, be demonstrated only for sural SNAP and SNCV and for tibial MNCV.*

*In a diabetic rat model, Pan et al demonstrated less impairment of sensory and motor nerve conduction velocities of the sciatic nerve in the electroacupuncture treatment group. Improved NCS values were accompanied by reduced myelinated nerve fiber damage and decreased proportions of cell apoptosis due to the ERS pathway, in comparison with a nontreatment group indicating structural enhancement. Our ACUDIN study confirms these findings on a clinical level. Because changes in nerve conduction studies are associated with neural fiber density differences, the observed improvement in NCS values indicates structural regeneration of nerve fibers. Hence, acupuncture might induce regenerative processes that could represent disease modification in DPN.*

*Clinical variables showed improvement in a number of subitems such as pain perception and localization of symptoms. However, NDS and NSS in total did not reach statistically significant changes during the study. Our study participants presented a mean age of 70 with a range of 42 to 89 years. Given that most patients suffered from progressed DPN and comorbidities including restrictions of mobility, we presume that higher clinical effects could be achieved in patients in earlier stages of DPN.*

*Tissue and nerve regenerative capacity has been shown to be decreased in diabetic patients. Acupuncture increases the blood flow in the extremities. The selected acupoints at the distal end of the extremities were chosen to improve the perfusion of the vasa nervorum and dependent capillary beds supplying local neurons. Shin et al demonstrated a positive effect of electroacupuncture on painful DPN,*

*using distal acupuncture points (Bafeng) as facultative points. All obligatory points were located proximal to the toes. There was a significant decrease in pain intensity as measured by NRS but no changes in NCS.*

*However, in the ACUDIN protocol, points located at the toes were obligatory (Bafeng and Qiduan). This approach resulted in significant changes in NCS values, suggesting that local microcirculatory effects could be the predominant mechanism of acupuncture-induced peripheral nerve repair, combined with modulation of cortical network connectivity contributing to the analgesic effect. In this context, needle acupuncture may represent a stronger stimulus than laser acupuncture.*

*Mild adverse events confirm that professionally administered local acupuncture is a safe treatment procedure in DPN conditions.*

*PROMs showed superior effects of needle acupuncture to placebo in all 12 variables and of laser acupuncture in 10 of 12 variables, reaching significance for hyperesthesia and cramps following needle acupuncture and for heat sensation following laser acupuncture.*

*Because these are pain-related symptoms, our results provide evidence for the value of acupuncture in pain therapy in DPN. Hyperesthesia and heat sensation can be signs of C-nociceptor hyperexcitability caused by fiber degeneration and alterations in channel expression, producing orthodromic and antidromic conduction and multiplication of spontaneously generated nerve impulses and receptor threshold reduction. Moreover, severity of muscle cramps in DNP correlates with small and large fiber measures. Hence, clinical improvement can be a sign of fiber repair, corresponding to positive NCS results in our study.*

*Nevertheless, PROMs showed fewer distinct group differences than NCS results together with higher evidence for placebo effects. This indicates the necessity to measure acupuncture effects by variables less susceptible to placebo, such as NCS."*

Here, yet another more recent study by some of the same researchers focusing on the impact of acupuncture on numbness and loss of sensory function so common and problematic in diabetics.

Hoerder S, Habermann IV, Hahn K, Meyer-Hamme G, Ortiz M, Grabowska W, Roll S, Willich SN, Schroeder S, Brinkhaus B, Dietzel J. Acupuncture in diabetic peripheral neuropathy-neurological outcomes of the randomized acupuncture in diabetic peripheral neuropathy trial. World J Diabetes 2023; 14(12): 1813-1823[12]

This study was a two-armed, randomized, controlled, parallel group, multicenter clinical trial with 62 participants with a mean age of 68 years. Twelve treatments were administered over eight weeks with standardized local acupuncture points of the lower extremities.

"*This trial focuses on hypesthesia/numbness and loss of further sensory functions, which is crucial in the development of gait disorders, risk of falls and development of diabetic foot. This approach is a novelty in DPN research, which usually concentrates on reducing pain or tingling. The reduction of numbness is of equally high importance since there is no pharmacological option for this symptom and it*

*is of high relevance in protecting the integrity of the feet. Our results showed the decrease of numbness at 8 and 16 wk to be above 32%, which is indicative of a clinically important improvement."*

Further, *"The trial adds the important information that a lasting improvement of DPN-related symptoms and improvement of sensory function can be achieved in chronically ill patients with an ongoing risk factor for neuropathy. The high adherence rate shows again that repetitive acupuncture treatments were well tolerated and led to patient satisfaction."*

In addition to giving details of the trials described above, we want to give an idea of the great number of RCTs done on acupuncture for DIPN by offering brief reviews of a number of recent systematic reviews on many of these RCTs. This also included reviews of multiple systematic reviews – the gold standard of the gold standard.

Before highlighting those systematic reviews we offer some context: We found an interesting dynamic that appears to be happening with the especially large number of systematic reviews regarding acupuncture taking place in China. In China, acupuncture is accepted as a legitimate therapy and has for years been well integrated into the Chinese mainstream healthcare system. This being the case, the way they have conducted their acupuncture research has focused on real world outcomes, i.e., "How effective is this therapy for this condition?" Their studies often do not conform to all the steps in the methodological guidelines researchers are encouraged to follow, such as the PRIMSA reporting guidelines or AMSTAR checklists for systematic reviews and CONSORT and STRICTA reporting guidelines for clinical studies to ensure low risk of bias.

There appears to be an effort in China to encourage their researchers to follow the types of research design and reporting guidelines that help to make RCTs and systematic reviews rated as having high reliability and low risk of bias. Many of the systematic reviews we found for acupuncture for DIPN rated the RCTs of low methodological quality stating - "acupuncture seems to be effective for DIPN but due to low methodological quality, the findings must be viewed with caution" or words to that effect.

Many of these reviews stress that these RCTs or systematic reviews would carry greater weight in supporting acupuncture's proven effectiveness if they would do a better job following these guidelines. They also state that their review gives specific suggestions for improvements in future RCTs and systematic reviews' design and methodology.

Of course, it would be better if the studies being reported from research done in China more closely followed these types of standards. Still, in the case of DIPN and CIPN, we believe the high percentage and sheer quantity of positive outcomes means that, despite their tendency to low methodological ratings, the importance of these finding should not be significantly downgraded. This is especially true when you consider studies like the idiopathic and DIPN studies we have highlighted or the CIPN ones we will soon highlight. Those studies followed these quality guidelines and reported similar successful outcomes to those found in the Chinese trials.

Lin T, Huang F, Zhao S, Qiu M, Wen J, Liu M. Acupuncture for diabetic peripheral neuropathy: An overview of systematic reviews. *Complementary Therapies in Clinical Practice.* 2021;43:101375.[13]

This study is a review of 18 systematic reviews on acupuncture for DIPN. The fact that there have been so many SRs on the use of acupuncture for this one condition is highly impressive. The SRs were published between 2011 and 2019, of which roughly 2/3 (64.7%) were published from 2016 to 2019, showing a significant increase in the number of SRs on this subject in recent years. The total number of RCTs in those 18 SRs is 307 and included a total of 22,872 test subjects. Although there was no doubt some overlap between the studies included in these 18 SRs this review still constitutes an impressively high number of published, peer-reviewed RCTs and a large number of test subjects.

In the Introductions section, the authors state flatly: *"Previous studies have proved that acupuncture produces positive effects on relieving symptoms of pain in patients with DPN."*

They further state: "*Acupuncture can increase the blood flow of peripheral nerve, accelerate the nerve conduction velocity and improve microvascular circulation."*

In the Conclusions section the authors state: "*All included SRs reported beneficial effects of acupuncture for DPN".* However, they then say these results should be taken with caution because of the *"limited methodological quality".*

Nash J, Armour M, Penkala S. Acupuncture for the treatment of lower limb diabetic peripheral neuropathy: a systematic review. *Acupuncture in Medicine : Journal of the British Medical Acupuncture Society.* 2019;37(1):3-15[14]

As systematic review of studies published in English up to 2017 on acupuncture for DIPN. Ten studies with 432 participants were included: three randomized controlled trials (RCTs), two pilot RCTs, three uncontrolled clinical trials, one quasi-RCT and one prospective case series.

All studies reported improvements in DPN pain symptoms.

Yu B, Li M, Huang H, et al. Acupuncture treatment of diabetic peripheral neuropathy: An overview of systematic reviews. *Journal of Clinical Pharmacy and Therapeutics.* 2021;46(3):585-598.[15]

Another review that included 18 systematic reviews. This review included 13 SRs in Chinese and 5 in English. The number of RCTs in each SR was between 7-16, with 112 RCTs studies included 8,378 subjects.

This review found most of the included studies measured total clinical efficacy rate and nerve conduction velocity. It further found that overall, acupuncture was effective in improving clinical effectiveness and nerve conduction velocity in the median nerve sensory and motor velocity and common peroneal nerve sensory and motor velocity (sections 3.5-3.5.5).

As we discussed above, this review rated the methodological quality of the included studies and found them to be "generally very low" and gave recommendations for improvements.

In the Discussion section it is stated:

*"The documents included in the current study did not provide preliminary plans, did not search the trial registration website and related grey literature, did not provide lists of documents excluded in the screening process, did not provide complete descriptions of the included studies and did not declare whether there were conflicts of interest. These problems may lead to omissions in screening, incomplete inclusion of the research, increased risk of bias in the research, publication bias and heterogeneity, which are all factors which heavily impact the research results. One particular problem with the included literature was that it did not explain the sources of heterogeneity or discuss its impact on the results, which affects the rigour of SRs as a basis for diagnosis and treatment. "*

Cho E, Kim W. Effect of Acupuncture on Diabetic Neuropathy: A Narrative Review. *International Journal of Molecular Sciences.* 2021;22(16):8575."[16]

This study reviewed 10 RCT's, 8 using manual acupuncture, 1 using electro-acupuncture, and 1 using manual and laser acupuncture. We believe this review can be especially helpful to CMS reviewers in that it gives details of each included RCT, including points used. It also reviewed five animal mechanism studies to shed light on the possible mechanisms behind the clinical improvements seen in clinical acupuncture studies including the potential for neuroregeneration.

"*In conclusion, based on the results obtained from all the included studies, we suggest that acupuncture could be considered a useful treatment method for diabetic neuropathy."*

# Presenting the Evidence Part Three
## Chemotherapy Induced Peripheral Neuropathy (CIPN)

Chemotherapy induced peripheral neuropathy (CIPN) is the second most common side effect of chemotherapy estimated to occur at a rate of 68.1% within the first month of chemotherapy treatment, 60.0% at three months, and 30.0% at six months (Seretny et al, 2014)[17]. A recent study "Mechanisms of Chemotherapy-Induced Peripheral Neuropathy" (Zajączkowska et al, 2019)[18] stated this issue succinctly:

*"Due to its high prevalence among cancer patients, CIPN constitutes a major problem for both cancer patients and survivors as well as for their health care providers, especially because, at the moment, there is no single effective method of preventing CIPN; moreover, the possibilities of treating this syndrome are very limited."*

While the specific type of nerve cell damage and mechanisms of onset can vary between the most common types of "stocking and glove" PN, in all these cases the nerve damage is considered to be irreversible and that is why the authors of the above quoted study said the *"possibilities of treating this syndrome are very limited".*

We have highlighted the acupuncture research that has employed before and after nerve conduction studies (NCS) for idiopathic and diabetic induced PN that found evidence suggesting that, with appropriate acupuncture therapy, the nerve damage in these PN cases is not necessarily irreversible. It is difficult to overstate what a breakthrough the prospect of nerve regeneration constitutes for PN suffers.

To start off our summation of the evidence for CIPN we will highlight another such study. We will then review a recent guideline "Integrative Medicine for Pain Management in Oncology" produced by the American Society of Clinical Oncology (ASCO) that investigated acupuncture for CIPN. Finally, we will review the studies on acupuncture for CIPN that were published since the ASCO study.

Friedemann T, Kark E, Cao N, et al. Acupuncture improves chemotherapy-induced neuropathy explored by neurophysiological and clinical outcomes – The randomized, controlled, cross-over ACUCIN trial. *Phytomedicine.* 2022;104:154294.[6]

In this study, the authors offer a helpful review of other acupuncture studies on CIPN that have used nerve conduction studies (NCS) and how their study sought to address the possible weaknesses is those other studies:

*"To date, nerve conduction studies (NCS) have not been widely used in clinical trials for CIPN. They have only been used as secondary outcome parameters. In addition, the examination is time-consuming, can be painful to the patient, and has to be performed by specialized neurologists to receive reliable results. Furthermore, studies that used NCS in CIPN trials for acupuncture had limitations because NCS was only implemented in a subgroup of volunteers (21 of 87 participants) (Molassiotis et al., 2019)[19], and*

*controlled after only four weeks of treatment (Iravani et al., 2020)[20], or where evaluation was restricted to nerve conduction velocities (Han et al., 2017)[21], whereas CIPN is characterized by predominantly sensory axonal degeneration (Quasthoff and Hartung, 2002). NCS can differentiate whether a neuropathy is axonal, demyelinating, or both and is generally accepted for the evaluation of the type and course of Peripheral Neuropathy. Furthermore, the effect of acupuncture has been verified by NCS in patients with diabetic neuropathy (Meyer-Hamme et al., 2020)[11]. Hence, we used NCS as the primary outcome parameter for the objectivation of expected acupuncture effects in the ACUCIN (Acupuncture for Chemotherapy-Induced Neuropathy) study. The goal of this study was to determine whether standardized body acupuncture improves NCS and reduces signs and symptoms in patients with CIPN".*

Here, the authors detail how the primary and secondary outcomes for sural nerve function was significantly improved and correlated to improvements in physical examination and patient-reported outcome measures (PROMS) but not for the less common motor nerve involvement:

*"The primary outcome parameter, sural SNAP, was significantly improved in the acupuncture group in comparison with the control group. Prior studies had shown, that an improvement of 1 µV correlates relevantly with a degree of myelinated fibre density comparable with an improvement of two points of the NDS (Russell et al., 1996). Hence, a difference of 2 µV found in our study should have functional relevance as was also shown by the parallel improvements in the physical examination, as well as with patient-reported outcome measures (PROMs).*

*Similar results were found for the secondary outcome parameter sural SNCV. NCS of the motoric tibial nerve did not show these improvements. However, in the presentation of CIPN sensory symptoms usually dominate (Kolb et al., 2016)[22], and in our study, only 13 of 60 participants showed mild motoric involvement in NCS on basement assessment."*

The authors further detail the many symptoms involved in CIPN, how these relate to different types of nerve damage, and which of these showed significant improvement with acupuncture and which only insignificant improvement. They also speculate that a longer treatment period may have made for better results due to the different length of time needed for different peripheral nerve regeneration:

"*All PROMs showed a clear trend in favour of acupuncture demonstrated in Fig. 6. Statistical relevance was reached for "burning pain" and "cramps". Burning pain can be secondary to C nociceptor hyperexcitability from fibre degeneration. This induces orthodromic as well as antidromic conduction and multiplication of spontaneously generated nerve impulses (Ochoa et al., 2005). Muscle cramps correlate as well as numbness with small-and-large fibre measures (Abraham et al., 2018). But not only did pain parameters reach statistical significance, but improvement in numbness also correlated with small-and-large fiber measures (Poncelet, 1998), as well as the steadiness of gait and the overall frequency of symptoms. The differences in improvements of the PROMs might be a sign of inhomogeneous regeneration of the peripheral nerve(s) and may become more homogeneous in a more extended treatment period.*

*Furthermore, distal pallhypesthesia was improved as measured by the Rydel-Seiffer tuning fork. Pallhypestesia is associated with large fiber degeneration (Poncelet, 1998). Examinations by physicians*

*revealed an improved "heel-to-toe walking" and improved "blind walking" in the acupuncture group compared to the waiting list. PROMs showed a significant improvement in unsteadiness of gait. Thus, this reduces the risk of falls (Kolb et al., 2016)[22], which is of specific relevance because there is no disease-modifying therapy."*

The authors then describe how this study's positive results relate to their previous studies on idiopathic and diabetic PN and how, since peripheral nerves "can only be destroyed in a limited number of ways", it is possible to use a standardized (or semi-standardized) acupuncture treatment protocol to trigger nerve regeneration in the different types of PN:

"*The data suggest that there is a positive effect of acupuncture on CIPN, similar to that shown prior to peripheral neuropathy of undefined aetiology (Schroder et al., 2007)[9] and diabetic neuropathy (ACUDIN) (Meyer-Hamme et al., 2020)[11]. Compared to ACUDIN, the effect of acupuncture on NCS, signs, and symptoms in this study were more pronounced. However, the population of this study was relevantly younger.*

*Despite different etiologies, the acupuncture concept was very similar in both studies. Given that the nerve can be destroyed only in a limited number of ways, the damage can only occur at the level of the axon or the myelin sheaths (Donofrio and Albers, 1990). Hence, enhancing the intrinsic regeneration potential of the peripheral nervous system is the goal of the treatment. The most imminent factor of the acupuncture concept is the use of local acupuncture points on the toes and fingers (Figs. 2 and 3), which other researchers have used with successful outcomes (Iravani et al., 2020;[20] Molassiotis et al., 2019[19]).*"

Finally, the authors mention a CIPN study some of these same authors were involved in (Rostock et al 2013)[23] that had a negative outcome. They suggest that not using local points may have been why that study was not successful:

*"Studies with negative results did not apply acupuncture needles locally (Rostock et al., 2013)[23]. The mechanism of this improvement is presumably the enhancement of peripheral circulation with an improvement of the perfusion of the vasa nervorum and dependent capillary beds supplying local neurons (Litscher et al., 2002) which encourages the removal of toxic agents and promotes neuroregeneration."*

In our review of the Rostock et al. study, we identified additional clinical protocols used in that study that were likely suboptimal. Those include treating only over a three-week period rather than a minimum of 10 weeks and utilizing electroacupuncture stimulation parameters that were suboptimal. We give more details of this Rostock study below when we consider the studies utilized in the ACSO guideline.

## The American Society of Clinical Oncology 2022 Guideline

In 2022, the ASCO reviewed and approved the findings of the Society of Integrative Oncology (SIO) and released a joint guideline titled "Integrative Medicine for Pain Management in Oncology'.[24] Although the

evidence that was considered in the development of this guideline was focused on pain, and acupuncture has the potential to help the other important non-pain symptoms associated with CIPN, considering the evidence they reviewed and the recommendations in this guideline is still helpful.

After considering the evidence that was used to develop the ASCO/SIO guideline including details of negative outcome studies, we will also detail several studies on acupuncture for CIPN that have been published since the publication of the studies used in that guideline's development.

The ASCO/SIO guideline recommendation was that acupuncture may be offered to patients with CIPN but stopped short of recommending that it should be offered. They noted that there were no serious side-effects and that most but not all of the studies they reviewed showed a benefit of acupuncture for CIPN.

The ASCO/SIO review included two systematic reviews (SRs); one consisting of 3 studies (Li et al.)[25] and the other consisting of 6 studies (Chien et al.).[26] They also reviewed 7 RCTs, but because some of the studies in the SRs were included in both reviews and some of the 7 RCTs were also in those SRs, the total number of studies included in their review was 9.

Seven of those nine studies showed positive benefit of acupuncture, one showed no benefit (Rostock et al.)[23] and one reported no benefit and expressed concern that the subjects in the real (verum) acupuncture arm had a slower recovery than the placebo (sham) acupuncture arm (Greenlee et al.)[27]. The Rostock study was included in both SRs while the Greenlee study was included in one (Chien et al).[26]

In Rostock et al.'s very small pilot study (EA group: n = 14), EA showed no difference from 3 controls—hydroelectric baths, vitamin B/vitamin B6, and placebo capsules. The researchers acknowledged that other studies on acupuncture for CIPN had positive findings and that several factors, including inadequate treatment dose, may have been confounding factors in this study. They cited a Schroder et al. 2007 study that advised that it can take up to 10 weeks of acupuncture to see measurable results in nerve conduction studies. In Rostock et al. study, participants received 8 + 1 treatments over 3 weeks.

Rostock et al. also stated, given that the goal of stable success for treating CIPN involves inducing neuroregeneration and that this can take from *''3 to 6 months,*" the effects of treatment would take longer than *''in other indications of acupuncture like pain or vegetative imbalance.''* These researchers also emphasized that *''our results only indicate that our particular standardized acupuncture protocol might not be effective in the treatment of CIPN, but the results cannot be generalized to other acupuncture concepts.''* This warning makes clear that, while it would be appropriate to include this study in a review investigating different EA protocols for treating CIPN, these results should not be included in systematic reviews investigating the larger question of acupuncture's effectiveness for treating CIPN. The electrostimulation parameters may also have been problematic. This study used 15 minutes of EA (50Hz) *''consisting of a combination of rectangular currents and high amplitude waves.''*

If one reads the whole Rostock study, one will see the authors make clear that this study was an outlier and only shows that their suboptimal protocols were ineffective contrary to other successful acupuncture trials on CIPN. We urge the CMS reviewers to not utilize this study in this NCD review.

The other negative outcome study included in the Chien SR[26]; the Greenlee, et al study,[27] was a pilot randomized trial of EA vs sham EA during active chemotherapy to investigate whether EA exerted a neuroprotective effect. There was no difference between groups in worst pain at Week 12 after employing 12, once-weekly treatments. At Week 16 (four-week follow-up) the sham group had improved compared to Week 12, but the EA group had worse pain than at Week 12. This led the researchers to express concern that the EA may have made the participants' pain worse and even to go so far as to recommend against further study of EA for CIPN prevention stating that further EA studies should focus only on treatment for established CIPN symptoms. However, other studies using higher treatment dosages investigating electro-acupuncture for preventing/reducing CIPN during active chemotherapy found no exacerbation of CIPN pain and some benefits, including one study, Zhang et al,[28] which was included in the Chien SR.[26]

Looking at the details of the six studies included in the Chien SR's Table 1, you can see that each of the four positive outcome studies[19,21,28,29] employed higher treatment dosages than were employed in both the Rostock[23] and Greenlee[27] studies. While the Greenlee study did just one treatment a week for 12 weeks during active chemo therapy, the Zhang study[28] employed seven daily treatments starting the day before chemotherapy then 14 days off with 21 days being a single "course" of treatment. Two consecutive courses were employed making 14 treatments delivered in two courses of 7 consecutive days.

The other three positive outcome studies[19,21,29], like the Rostock study, were for the treatment of already established CIPN post-chemotherapy. Unlike the Rostock study, these three employed manual (not electric) acupuncture. Two of those positive outcome studies employed 18 treatments over eight weeks.[29] The other employed 24 treatments over 12 weeks.[21]

In Table 1 of the Li SR, again it was reported that the two positive outcome studies[21,29] employed a higher dosage of treatments; one study using 3 times a week treatments for 12 weeks[21] and the other 2-3 weekly treatments over eight weeks for a total of 18 treatments[29]. Those two positive outcomes studies also employed manual acupuncture.

## Factoring-in the Potential Impact of Neuroregeneration

The most curious aspect of the Greenlee study[27] was how the subjects in the true EA arm of the study had pain levels equal to the sham EA subjects when both the acupuncture therapy and chemotherapy ended at week 12 but the true EA subjects had their pain increase (equal to about 1 point in a 1-10 pain scale) while the sham EA subjects had their pain levels decrease about the same amount. While the study's authors offered possible explanations for this surprising finding, one thing they did not discuss was the possibility of neuroregeneration.

Acupuncturists experienced in treating PN report that patients often undergo a phase of neuroregeneration when pain sensitivity increases before settling back down like a foot that has "fallen asleep" starting to wake back up before feeling normal again. An exacerbation of pain at Week 16 as in

this Greenlee study may have been part of the normal course of nerve regeneration, and hence should not necessarily be interpreted as a negative outcome.

Experienced acupuncture clinicians learn to warn their patients that they may experience a temporary phase of increased discomfort when their nerve functions start to improve. It seems appropriate that this information should be included in the informed consent test subjects agree to when involved in trials of acupuncture treating PN. When assessing the possibility of nerve regeneration in CIPN it is important that pain is interpreted within the context of the normal course of nerve regeneration. This includes follow-up timeframes which capture the whole picture of neuroregeneration over the course of three to six months.

While many aspects of the Greenlee study were well designed, it may have been the low dosage of once weekly treatments during active chemotherapy that was the reason for the negative outcome. Although their use of once weekly treatments over 12 weeks should have been enough to measurably reduce symptoms in already established CIPN, it may well be that higher treatment dosages would be needed to prevent or reduce the onset of CIPN during active chemotherapy.

In our review of dozens of studies of acupuncture for the various types of PN, there were some positive outcome studies that employed relatively lower treatment dosages. However, we found no negative studies that employed relatively higher treatment dosages – more than once weekly treatments over eight weeks or longer or daily treatments over shorter timeframes. This suggests that while relatively lower treatment dosages may be effective in some cases, a higher treatment dosage increases the odds of successful outcomes.

It simply cannot be overstated how important the treatment dosage – the spacing and total number of treatments over time – can be to the outcomes with acupuncture therapy. Acupuncture is a therapy that has the potential to facilitate homeostasis by helping the body to better modulate bodily resources, i.e. body chemistry such as improved local blood flow facilitating neuroregeneration. This being the case, every acupuncture treatment is potentially like taking a dose of a medication and so, as is the case when assessing the effectiveness of medications, trying to understand and utilize the optimal treatment dosage is paramount in acupuncture therapy.[7]

The pattern in acupuncture research of relatively higher success rates with higher treatment dosages and relatively higher failure rates with lower dosages is there to be found to anyone who seriously investigates this. It is certainly the case in the studies considered in the ASCO/SIO guideline review and in the studies and SRs published since that review. We urge the CMS reviewers to give due consideration to the treatment dosage in acupuncture studies when doing this NCD review or any review of acupuncture. This will not only inform CMS reviewers on the issue of acupuncture's benefit-to-harm ratio in treating PN, but also the number of treatments over what period of time should be authorized.

In summation, although the ASCO/SIO did recommend that acupuncture "may be offered" for treating the pain associated with CIPN, they did not give the strongest recommendation stating the acupuncture "should be offered". However, this recommendation was based on studies they reviewed that included two negative outcome studies, one of which – Rostock - clearly should not have been included in any SR

considering the overall efficacy of acupuncture for CIPN. The second negative study, Greenlee, was considering electroacupuncture for preventing CIPN and employed a treatment dosage that might have been appropriate for treating established CIPN but was perhaps not enough for preventing CIPN during active chemotherapy.

## CIPN Studies Published Since the ASCO/SIO Guideline

The ASCO/SIO review included studies published up to 2020. Since that time, we found an additional 7 RCTs and 4 SRs that have been published that investigated acupuncture for CIPN. Out of the 7 RCTs six were positive and only one was negative. All of the 4 SRs reported positive outcomes. We offer the following thoughts on why the one study had negative outcomes due to problems in clinical protocols.

The lone negative RCT by Hammond, et al., had a rather declarative title: "Electro Acupuncture is not Recommended for Managing Chronic Neuropathic Pain in Chemotherapy Induced Peripheral Neuropathy: A Double Blind Randomized Controlled Trial".[30]

This was actually quite a small pilot study (10 subjects in the true EA group and nine subjects in the sham EA group), and the subjects were given once a week treatment for six weeks. While the authors cited their small sample size as a limitation of the study, unlike Rostock, they did not cite their low treatment dosage as a limitation. And, while the authors did point out that their negative findings were based on true EA *"at these stimulation and treatment parameters",* one would not glean that limitation from the study's title.

Like the Rostock study, we feel this Hammond study should only be viewed as having value in a review comparing different EA protocols for treating CIPN and should not be considered in any review, such as this NCD, trying to determine acupuncture's overall efficacy in treating CIPN. This is probably also the case for the Greenlee study for the reasons we cited above.

## Summation of findings of the studies on acupuncture for CIPN published since the ASCO/SIO guideline review

1. Huang CC, Ho TJ, Ho HY, et al. Acupuncture Relieved Chemotherapy-Induced Peripheral Neuropathy in Patients with Breast Cancer: A Pilot Randomized Sham-Controlled Trial. *Journal of Clinical Medicine.* 2021;10(16):3694.[31]

Conclusions: It is concluded that manual acupuncture alleviated neuropathic pain in CIPN. In addition, manual acupuncture was effective in improving touch perception thresholds, as assessed by SWM. The current results did not reveal that acupuncture improves the quality of life of patients with cancer. This warrants further large-scale clinical trials in the future.

2. Huang MC, Chang SC, Liao WL, et al. Acupuncture May Help to Prevent Chemotherapy-Induced Peripheral Neuropathy: A Randomized, Sham-Controlled, Single-Blind Study. *The oncologist.* 2023;28(6):e436-e447.[32]

Implications for Practice: The results of this clinical trial indicate that acupuncture given concurrently with oxaliplatin protects against the often-debilitating chemotherapy-induced peripheral neuropathy (CIPN) in stage 3 colorectal cancer. Verum acupuncture was more protective than sham acupuncture upon touch thresholds in the prevention of CIPN. The beneficial effect of acupuncture upon the touch threshold endured for at least six months after completion of the intervention.

3. Stringer J, Ryder WD, Mackereth PA, Misra V, Wardley AM. A randomised, pragmatic clinical trial of ACUpuncture plus standard care versus standard care alone for Chemotherapy Induced Peripheral Neuropathy (ACUFOCIN). *European Journal of Oncology Nursing.* 2022;60:102171.[33]

Conclusion: A 10-week course of acupuncture resulted in measurable improvement in participants symptoms of CIPN. The results warrant further investigation.

4. Chan K, Lui L, Lam Y, et al. Efficacy and safety of electroacupuncture for oxaliplatin-induced peripheral neuropathy in colorectal cancer patients: a single-blinded, randomized, sham-controlled trial. *Acupuncture in Medicine : Journal of the British Medical Acupuncture Society.* 2022:9645284221125421[34]

Conclusion: This study showed preliminary evidence for the efficacy and safety of EA in acute CIPN among CRC patients, although further studies are needed to verify these effects and to further explore the potential role of EA in chronic CIPN (effects on which remain unclear).

5. Ben-Arye E, Hausner D, Samuels N, et al. Impact of acupuncture and integrative therapies on chemotherapy-induced peripheral neuropathy: A multicentered, randomized controlled trial. *Cancer.* 2022;128(20):3641-3652.[35]

Conclusions: Acupuncture, with or without CIM modalities, can relieve CIPN-related symptoms during oncology treatment. This is most pronounced for hand numbness, tingling, pain, discomfort, and for physical functioning.

6. Hwang MS, Lee HY, Choi TY, et al. A systematic review and meta-analysis of the efficacy of acupuncture and electroacupuncture against chemotherapy-induced peripheral neuropathy. *Medicine (Baltimore).* 2020;99(17):e19837.[36]

SR - Conclusion: Acupuncture is safe, but the symptom-alleviating effect on CIPN can hardly be determined because of methodological deficiencies of the included studies. In terms of the clinical efficacy rate, acupuncture was more effective than conventional pharmacological treatments

7. Zhao YX, Yu XC, Gao JH, Yao MJ, Zhu B. Acupuncture for Paclitaxel-Induced Peripheral Neuropathy: A Review of Clinical and Basic Studies. *Journal of Pain Research.* 2021;14:993-1005[37]

SR - In conclusion, acupuncture could be considered as a potential alternative therapy in treatment of PIPN, and further clinical and experimental studies are called for in the future.

8. Zhang XW, Hou WB, Pu Fl, et al. Acupuncture for cancer-related conditions: An overview of systematic reviews. *Phytomedicine.* 2022;106:154430.[38]

Overview SRs. Conclusion: Evidence from SRs showed that acupuncture is beneficial to cancer survivors with cancer-related pain, fatigue, insomnia, improved quality of life, nausea and vomiting, bone marrow suppression, menopausal symptoms, arthralgia, and dysphagia, and may also be potential for lymphoedema, gastrointestinal function, and xerostomia. For neuropathy, depression and anxiety, acupuncture should be used as an option based on individual conditions. Acupuncture is relatively safe without serious adverse events. More well-designed clinical trials of acupuncture are recommended on cancer-related depression and anxiety, arthralgia, xerostomia, gastrointestinal dysfunction and dysphagia.

9. Jin Y, Wang Y, Zhang J, Xiao X, Zhang Q. Efficacy and Safety of Acupuncture against Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis. *Evidence-based complementary and alternative medicine : eCAM.* 2020;2020:8875433.[39]

SR Conclusion. The use of acupuncture in the management of CIPN is safe and effective. The most used acupoints for CIPN are LI 4, LI 11, ST 36, M-LE-8 (Bafeng), and M-UE-22- (Baxie).

10. Friedemann T, Kark E, Cao N, et al. Acupuncture improves chemotherapy-induced neuropathy explored by neurophysiological and clinical outcomes – The randomized, controlled, cross-over ACUCIN trial. *Phytomedicine.* 2022;104:154294.[6]

This study we reviewed in detail in the previous section

Conclusion: Acupuncture can enhance structural regeneration in CIPN as measured by NCS, which is manifested in subjective improvement and neurological findings.

11. Hammond EA PM, Lambert P, Shay B Electro Acupuncture is not Recommended for Managing Chronic Neuropathic Pain in Chemotherapy Induced Peripheral Neuropathy: A Double Blind Randomized Controlled Trial. *J Orthop Res Ther* 2022;7:1266.[30]

This study we reviewed in detail earlier in this section.

Conclusion: This trial used best practice, incorporated a homogeneous population, used valid and reliable outcome measures, and sham controls. The evidence suggests that EA does not provide superior analgesia compared to placebo acupuncture and may reduce the placebo response.

# Presenting the Evidence Part Four
## Peripheral Neuropathy Associated With HIV/AIDS (HIV PN)

There are few studies that have been conducted on acupuncture's effectiveness in treating PN associated with HIV/AIDS patients. One study published in 1998 (Shlay et al[40]) found acupuncture was not effective. However, another study (Schiflett et al, 2011[41]) further investigated the Shlay et al. study and found multiple issues with the way it was conducted and reported.

Essentially, Schiflett et al. found that there were three studies that had been combined and *analyzed "with a relatively insensitive statistics"*. The negative outcome was in one study where acupuncture treatment was combined with amitriptyline. The reanalysis found *"there may have been adverse events associated with the combination of the two treatments"*. When analyzing the studies in which acupuncture was used without being combined with amitriptyline *"acupuncture was clearly effective in reducing attrition and mortality"* although mixed for pain.

A 2013 study (Anastasi et al[42]) investigated acupuncture combined with the heat therapy known as moxibustion or "moxa", that involves burning the dried herb artemisia vulgaris (mugwort). They reported: "*The participants in this study began with pain severity one to two levels more severe than moderate: barely strong to slightly intense. The reduction in the GPS score for the Acu/Moxa group was 0.25 points (reduced by two pain levels) immediately following weeks of twice weekly treatment sessions and 0.36 points (reduced by three pain levels) at the third follow-up visit, after 9 weeks without further treatment: almost twice the reduction observed in the Sham/ Placebo of 0.18 and 0.20 (reduced by one pain level), respectively. The benefit of Acu/Moxa was superior to Sham/Placebo at the first follow-up visit ($p < 0.05$), 3 weeks after the cessation of treatment, and retained a trend toward superiority at the second and third follow-up visits ($p < 0.10$). This pattern suggests that Acu/Moxa not only provided a reduction of pain during treatment but also provided relief for the duration of the nontreatment follow-up phase studied here."*

While the number and quality of studies done on acupuncture for HIV PN are not as robust as is the case for DIPN and CIPN, there is good reason to believe that acupuncture can be effective for HIV related PN. As was highlighted in the section on CIPN, peripheral nerves *"can only be destroyed in a limited number of ways"* and acupuncture has been shown to be effective in treating that nerve damage.

# Presenting the Evidence Part Five
## Further Considerations

### Acupoints Most Frequently Used in Treating PN

We mentioned in the introduction that there have been several studies regarding acupuncture treatment for PN that investigated what acupuncture points were the most commonly used in successful outcome studies and that these studies found that local points were most commonly used. Among the most recent and thorough of these types of reviews was an umbrella review of 9 SRs/MA for CIPN.[43] These researchers found that for the lower extremities (stocking area of symptom distribution), the most commonly used points were Stomach 36 (ST 36), Liver 3 (LR 3) and Spleen 6 (SP 6) while for the upper extremities points Large Intestine 11 (LI 11) and Large Intestine 4 (LI 4) were the most commonly used. Those same lower extremity points were also found in another recent review: *"Data mining analysis reveals key acupoints and meridians for the treatment of chemotherapy-induced peripheral neuropathy"*.[44]

Another review, "The Case for Local Needling in Successful Randomized Controlled Trials of Peripheral Neuropathy: A Follow-Up Systematic Review",[45] looked at many different types of neuropathy including mono-neuropathies like Bell's palsy and Carpal Tunnel syndrome. In the case of distal polyneuropathies such as is the focus of this NCD review request, the authors reported: *"The majority of the used acupuncture points are in close anatomical correlation with distal nerves in the arm and leg and each used point could be correlated to a large peripheral nerve or its branch."*

Other studies that review the most comply used acupuncture points that CMS reviewers may want to consider include: Zhao et al 2021[37] and Jin et al 2020[39].

### The role of microcirculation and neurotrophins in the effects of acupuncture and EA on neuroprotection and neuroregeneration

Some researchers have suggested that the mechanism by which acupuncture stimulates regeneration of peripheral nerves is associated with improving peripheral microcirculation[6,13]. Numerous studies demonstrate that acupuncture can improve peripheral microcirculation in a variety of contexts by increasing production and release of vasodilators such as nitric oxide.[46,47] While this is feasible, more recent research suggests that acupuncture's ability to regulate neurotrophins might be more relevant.

Acupuncture has been shown to be capable of upregulating or downregulating neurotrophins, especially BDNF (brain-derived neurotrophic factor). In allergy, it is clinically useful to reduce the elevated levels of neurotrophins which exacerbate the acute allergic inflammatory response[48-50]. In PN, acupuncture can increase the levels of neurotrophins to promote peripheral axonal nerve growth. [51-53]

A review by Lin et al stated that *Acupuncture can inhibit neurodegeneration via expression and activation of BDNF*.[51] In a recent review on diabetes and depression comorbidity, acupuncture and related techniques were found to significantly increase neurotrophins including BDNF, insulin-like growth factor-

1 and NT-3 in diabetics. (Zhang 2023).[54] Improvements in nerve conduction studies (which have been shown in numerous acupuncture and EA studies) confirm that acupuncture and EA can stimulate the regeneration of peripheral nerves. It appears that this neuroregeneration is mediated mainly by neurotrophins, although it is also possible that improving microcirculation (by upregulating vasodilators such as nitric oxide – a demonstrated effect of acupuncture) may also play a role.

## Number of Approved Treatments and Qualifications of Acupuncturists.

In its January 21, 2020 Decision Memo CAG-00452N "Acupuncture for chronic low back pain", the CMS detailed how many acupuncture treatments would be covered and the qualifications of those allowed to furnish the acupuncture treatments.

CMS allowed up to 12 acupuncture treatments over 90 days and then up to an additional 8 treatments for patients demonstrating improvement.

For Medicare beneficiaries suffering from peripheral neuropathy, we urge the CMS to allow for a modestly higher number of treatments in a more compressed timeframe.

While one treatment a week for a minimum of 10 weeks has been found to produce measurable benefits for PN sufferers, many studies in China found better results with more frequent treatments. It is especially beneficial to start these treatments with a higher frequency of at least twice a week for the first 3-4 weeks before reducing to once weekly.

Therefore, we ask CMS to allow 12 treatments within 60 days then another 12 treatments if improvements are demonstrated for a total of 24 treatments a year. Even this number is on the low end of optimal treatment dosage for PN sufferers but will afford the potential for better results than the treatment numbers allowed for chronic low back pain. For more on treatment dose in acupuncture therapy please see: "Is acupuncture dose dependent? Ramifications of acupuncture treatment dose within clinical practice and trials."[7]

In that same Decision Memo the CMS described who may furnish acupuncture as:

"Physicians (as defined in 1861(r)(1)) may furnish acupuncture in accordance with applicable state requirements.

Physician assistants, nurse practitioners/clinical nurse specialists (as identified in 1861(aa)(5)), and auxiliary personnel may furnish acupuncture if they meet all applicable state requirements and have:

A masters or doctoral level degree in acupuncture or Oriental Medicine from a school accredited by the Accreditation Commission on Acupuncture and Oriental Medicine (ACAOM); and

current, full, active, and unrestricted license to practice acupuncture in a State, Territory, or Commonwealth (i.e. Puerto Rico) of the United States, or District of Columbia.

Auxiliary personnel furnishing acupuncture must be under the appropriate level of supervision of a physician, physician assistant, or nurse practitioner/clinical nurse specialist required by our regulations at 42 CFR §§ 410.26 and 410.27."

The manner in which the CMS describes the qualifications of who may furnish acupuncture was unclear and has led to problems in the ability of Medicare beneficiaries to actually get treatment for chronic low back pain. That description does not mention the types of providers who would typically have the highest required level of training and competency testing, i.e. Licensed Acupuncturists. It is also unclear whether CMS will allow this type of provider to furnish acupuncture if they are not licensed as physician assistants or nurse practitioners/clinical nurse specialists (as identified in 1861(aa)(5)). CMS makes it clear that it will allow physicians to furnish acupuncture "in accordance with applicable state requirements." However, most states do not require physicians to have any training or pass any competency exams in acupuncture.

We understand that the laws regarding what types of providers can legally practice acupuncture vary from state to state. We also can appreciate that your standards for who can furnish acupuncture may get more complicated due to Medicare billing requirements. CMS states that "Auxiliary personnel furnishing acupuncture must be under the direct supervision of a physician, physician assistant, or nurse practitioner/clinical nurse specialist." It seems the "auxiliary personnel" could be a "Licensed Acupuncturist", although this is not explicit. The vast majority of acupuncture treatments carried out in the U.S. are performed by Licensed Acupuncturists in private practice or in small clinic settings where there is no direct supervision by physicians, physician assistants, or nurse practitioners/clinical nurse specialists.

We urge the CMS to work with the professional associations that represent Licensed Acupuncturists such as the American Society of Acupuncturists to better define who may furnish acupuncture to Medicare beneficiaries.

CMS should at least drop the provision that those furnishing acupuncture must have "A masters or doctoral level degree in acupuncture or Oriental Medicine from a school accredited by the Accreditation Commission on Acupuncture and Oriental Medicine (ACAOM)".

The only requirement the CMS should stipulate is that acupuncture providers have "current, full, active, and unrestricted license to practice acupuncture in a State, Territory, or Commonwealth (i.e. Puerto Rico) of the United States, or District of Columbia."

Requiring degrees from schools accredited by the ACAOM leaves out thousands of highly qualified and experienced Licensed Acupuncturists that graduated from state approved acupuncture schools when those states did not require ACAOM accreditation. The CMS should work with the acupuncture profession to increase the availability of qualified acupuncturists so that Medicare beneficiaries will have more access to care. This is especially true for Medicare beneficiaries living in rural or otherwise underserved areas where finding qualified acupuncturists is already a challenge.

## Thank You

We wish to thank the Centers for Medicare and Medicaid Services and their staff for their consideration of this National Coverage Determination request.

We are also thankful for the help of the following individuals in preparing this request: Ann Bailey, Elizabeth Hammond, Bill Reddy, Elad Schiff, and Sven Schröder.

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## Summary of acupuncture trials for peripheral neuropathy

### Cohort/observational studies

| Study | Condition | Study type | Number of subjects | Outcomes |
|---|---|---|---|---|
| Abuaisha et al 1998[55] | DPN | **Cohort study**<br>6 courses over 10 weeks | n = 46 | Symptomatic improvement<br>No change in peripheral neurological examination scores, VPT or in HbA1c |
| Schroder 2007[9] | PN of undefined aetiology | **Observational study** over I year<br>Acup vs standard care | n = 47<br>21:26 | Symptoms and NCS<br>Acup: 16 improved (symptoms & NCS), 3 no change, 2 worse<br>Standard care: 4 improved, 7 no change, 15 worse<br>Importantly, subjective improvement was fully correlated with improvement in NCS in both groups. The data suggest that there is a positive effect of acupuncture on PN of undefined etiology as measured by objective parameters. |
| Bailey et al 2017[56] | DPN | **Cohort study**<br>Acupuncture weekly for 10 weeks | n = 19/25 | The Neuropathy Total Symptom Scale<br>(NTSS-6), Neuropathy Disability Score (NDS), and laser Doppler fluxmetry (LDF) were used for assessment at baseline and 10 weeks. A total of 19 of 25 study participants completed the study and reported a significant reduction in the NTSS symptoms of aching pain, burning pain, prickling sensation, numbness, and allodynia. Lancinating pain did not decrease significantly. LDF measures improved but not significantly. |
| Bao et al 2018[57] | CIPN (breast) (placitaxel) | **Cohort study -** Single-arm Phase IIA to measure prevention of developing from grade II CIPN to grade III CIPN during active chemo<br>Acup median 3 sessions, range 1-11 sessions | n = 27 | 26/27 did not develop grade III CIPN during chemo<br>FACT-GOG/Ntx and NPS scores<br>Secondary: vibration, plasma BDNF (no change) |

### Randomized controlled trials (RCTs) - Pilot studies and substudies

| Study | Condition | Study type | Number of subjects | Outcomes |
|---|---|---|---|---|
| Tong et al 2010[58] | DPN | **RCT (Pilot)**<br>Daily acup vs "sham acup" for 15 days | n = 63<br>42:21 | F-wave minimum latency, MNCV & FCV in median and tibial nerves: |

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| | | Sham was same points needled to depth of 0.3cm with no manipulation (to avoid deqi) | | Forearm and distal SNCV improved in acup group (forearm SNCV was significant change)<br>No changes in motor or sensory nerves in sham group<br>VPT (Vibration perception threshold) improved both pre and post in acup group and between acup and sham<br>Significant improvement in extent and severity of numbness, pain and rigidity in acup group, no change in sham |
| Penza et al 2011[59] | DPN, IPN | **RCT (crossover) (Pilot - undeclared)**<br>EA vs "sham EA" (same EA stimulation on "neutral anatomical points close to the acupoints") with crossover<br>6 sessions every 5-7 days, 12 weeks washout<br>EA – biphasic square wave for 30 minutes (2-10 Hz) | n = 16<br>11:5 | VAS, BDI, SF-36 QOL, Patient's Global Impression of Change (PGIC)<br>Acupuncture vs.control: No significant difference after treatment<br>Post vs. preintervention: No significant difference compared to baseline in either group<br>No significant difference based on order of treatment |
| Lu et al 2012[60] | CIPN (ovarian cancer) (mainly carboplatin and paclitaxel) | **Substudy** to explore effects of acup on QoL during chemotherapy<br>Acup and EA 20-25 Hz for 30 mins: 10 treatments 2-3 x weekly over 4 weeks vs sham – nonpoints connected to inactivated EA beginning 1 week before cycle 2 of chemo | n = 21<br>11:10 | EORTC-QLQ-C30 – subscores for social function, pain and insomnia improved in acup/EA only; after adjustment for baseline differences only social function improvement was significant<br>QLQ-OV28 – no significant differences |
| Greenlee et al 2016[27] | CIPN (breast cancer) (taxane) prevention and treatment | **RCT (pilot)** EA vs sham<br>EA weekly for 12 weeks 2 Hz for 30 mins during active chemo<br>Park sham needles on non-points during chemo | n = 63<br>31:32 | BPI-SF: Worst pain score increased at week 12<br>EA: 2.6 vs Sham: 2.8<br>Week 16 - EA: 3.40 vs Sham: 1.7<br>FACT-NTX – no differences; trend to worse pain at week 16<br>FACT-TAX – no differences<br>NPS – EA worst pain 4<br>Future studies should focus on electroacupuncture or other forms of acupuncture for the treatment as opposed to prevention of CIPN. |
| Lu et al 2019[29] | CIPN in breast cancer (taxane) | **RCT (pilot)**<br>18 acup over 8 weeks<br>Vs usual care 8 weeks; 9 acup over 8 weeks<br>Manual acup first week then EA 2-10Hz | n = 40<br>20:20 | Statistical and clinical significant improvements in neuropathic pain and paraesthesia |
| Bao et al 2020[61] | Moderate to severe CIPN solid tumours (breast & colorectal) | **RCT (pilot)**<br>Real vs sham vs usual care for 8 weeks<br>Real acup: manual body + ear + EA (LR 2 - GB 42: 2-5 Hz for 20 mins)<br>Sham: non-insertion, non-points | n = 75<br>27:24:24 | NRS week 8: Real -1.75, Sham -0.91 , Usual -0.19<br>NRS week 12: Real -1.74, Sham -0.34 |

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| Hammond et al 2020[30] | CIPN in primary breast cancer (taxane) | **RCT (pilot - undeclared)**<br>EA 2Hz for 30 mins on LI 4, LR 3, ST 36 weekly for 6 weeks<br>Sham: Streitberger with inactivated EA on same points. Failed to acknowledge active sham<br>**Hints at possible harm but no harm was demonstrated** | n = 19<br>10:9<br>No power calculation | Primary: NPRS, questionnaires (S-LANSS)<br>Secondary: QST<br>EA: NPRS 5.0 (4.75-6.0) to 4.25 (3.25-5.0)<br>Sham: NPRS 5.5 (3.5-7.75) to 2.5 (2.0-3.0)<br>**None of the participants were worse** with the majority having decreased pain scores post-treatment compared to baseline.<br>QST – no change<br>70% of participants in the true (n= 7) and 75% of sham group (n= 6) believed acupuncture had improved their pain.<br>Described as "double blind" but was actually participant and assessor blinded.<br>One sham group withdrew as she said acupuncture made her pain worse.<br>Comparison of the post treatment S-LANSS scores between the sham and true groups were not significant<br>***"We had concerns that EA potentially may be maintaining the neuropathic pain."***<br>*"The evidence suggests that EA does not provide superior analgesia compared to placebo acupuncture and may reduce the placebo response."* |
| Iravani et al 2020[20] | CIPN cancer type not specified<br>Chemo not specified | **RCT (pilot)*** 12 manual acup over 4 weeks (deqi)<br>vs Vit B and gabapentin<br>*Although the sample size met the power calculation the authors still described this study as a pilot study | n = 40<br>20:20<br>Power calculation 16 per arm | Nerve conduction studies (NCS) – acup improved; medication did not<br>Numerical rating scale (NRS) both improved, acup more than medication<br>Adverse events decreased significantly: acup more than medication<br>Patient satisfaction higher in acup group |
| Huang et al 2021[31] | CIPN breast cancer (taxane) | **RCT (pilot)** verum vs sham acupuncture<br>15 treatments over 9 weeks | n = 20<br>10:10 | Touch perception thresholds measured with Semmes–Weinstein monofilament testing (SWM): verum acupuncture group had more improvement than sham group.<br>Average pain severity measured with Brief Pain Inventory-Short Form (BPI-SF): verum acupuncture group was significantly lower than sham group.<br>No significant differences in the |

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| | | | | FACT/GOG-Ntx trial outcome index and WHOQOL-BREF scores between groups. The results suggest that acupuncture can alleviate the neuropathic pain of CIPN and improve touch perception thresholds. |
| Mackereth et al 2023[62] | CIPN | **Qualitative substudy** nested within an RCT of n =120 acup vs waitlist | n = 23 | |

## Randomized controlled trials (RCTs)

| Study | Condition | Study type | Number of subjects | Outcomes |
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| Zhang et al 2010[63] | DPN | **RCT (unblinded)**<br>Acup vs oral inositol over 3 months<br>14 sessions daily per course, for 5 consecutive courses with a 4-day interval between courses. (70 sessions) | n = 65<br>32:33 | Acup: 16 markedly relieved, 12 improved, 4 failed<br>Control: 7 markedly relieved, 14 improved, 12 failed |
| Rostock et al 2013[23] | CIPN<br>mixed cancer types and chemo types | **Four-arm RCT (unblinded)**<br>EA vs hydroelectric baths, vs Vit B1/B6 vs placebo capsules<br>EA: 8±1 EA treatments: 15 minutes of EA (50Hz) consisting of a combination of rectangular currents and high amplitude waves<br>3 week treatment and observation period | n = 59<br>14:14:15:17 | Questionnaire, NRS, neuropathy score, CTC, QoL (EORTC QLQ-C30)<br>EA, HB Vit B similar effects to placebo |
| Han et al 2017[21] | CIPN<br>Multiple myeloma | **RCT**<br>Acup 3 cycles of daily for 3 days then alternate days for 10 days + methylcobalamin<br>vs methylcobalamin alone | n = 104<br>52:52 | VAS, QoL, NCS<br>NCS: Motor conduction velocity (MCV)<br>Sensory conduction velocity (SCV)<br>MCV of median and peroneal nerves improved signifciantly in Acup + Meth group but not in control<br>SCV of sural nerve improved sigificantly (but not in median nerve) in Acup + Meth; control no change |
| Zhang et al 2017[28] | CIPN<br>All Cancers<br>Mixed chemo | **RCT**<br>Acup vs EA (sparse-dense wave, with a frequency of 2-100 Hz): 2 courses of daily for 7 days, then 14 days off | n = 40<br>20:20 | QoL (KPS), TCM s&s, immune status (NK, CD3+,CD4+,CD8+, CD4+/CD8+)<br>EA improved CIPN, QoL (KPS) but no effect on immune function<br>Acup improved CIPN and QoL (KPS) but no effect on immune function<br>EA superior to acup in improving QoL, KPS, CIPN |
| Shin et al 2018[64] | PDN<br>(painful diabetic neuropathy) | **RCT (Multi-center)** in Korea<br>EA: 2/120Hz - 2 x weekly for 8 weeks<br>vs no EA treatment | n = 126<br>63:63 | Improved PI-NRS scores (-0.67 vs. control) at week 9, continued to improve at Week 13, plateaued at Week 17 |

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| | | | | Percentage of responders (≥50% pain reduction from baseline) in EA group continued to increase from Week 5 to Week 17.<br>Improved short-form McGill pain Q., sleep interference scores, and EuroQol-5 Dimensions Q. at week 9<br>No change in NCV<br>No difference in adverse events between groups so safe and well-tolerated<br>These findings suggest that EA treatment<br>may be recommended as a nonpharmacological treatment for pain<br>reduction in PDN. |
| Molassiotis et al 2019[19] | CIPN<br>All Cancers<br>Mixed chemo | **RCT** randomised assessor-blinded controlled trial<br>Manual acupuncture vs waitlist (usual care)<br>Acup 2x weekly for 8 weeks | n = 87<br>44:43 | Significant changes in pain intensity and pain interference<br>Significant improvement in TNSc (combination of sensory tests/neurological assessment, signs and symptoms)<br>Significant improvement in FACT/COG/NTX subscales for physical wellbeing, functional wellbeing and neurotoxicity |
| Meyer-Hamme et al 2021[11] | DPN | **RCT**<br>Manual acupuncture vs laser acupuncture vs sham acupuncture<br>10 sessions over 10 weeks<br>Follow up at Week 15 | n = 180<br>60:60:60 | Primary: Sural SNAP<br>Secondary: other NCS, clinical scores, PROMs<br>Sural SNAP and sural and tibial NCVs improved more in acup than sham<br>Acup faster onset than laser<br>PROMs acup & laser superior to sham<br>Our findings are evidence that acupuncture is an appropriate safe, nonpharmacological complementary treatment option for type 2 diabetic patients with DPN. |
| Stringer et al 2022[33] | CIPN (mixed cancer types and chemo types) | **RCT -** Randomised pragmatic clinical trial<br>Acup + standard care (SC) [medication] vs standard care alone<br>Acup once weekly for 10 weeks | n = 120<br>60:60 | 68% "success" in acup + SC<br>33% "success" in SC<br>Success was ≥ 2 point improvement on MYMOP2 |
| Friedemann et al 2022[6] | CIPN (mixed cancer types and chemo types) | **RCT** crossover; blinded assessors<br>Acup, 4 week washout then waitlist vs<br>Waitlist, 4 week washout then acup<br>10 weeks, 10 treatments | n = 60<br>30:30<br>Power calculation 27 per arm | Nerve conduction studies (NCS)<br>Subjective improvement (NRS)<br>Physical exam<br>Sural sensory nerve amplitude, and sural nerve conduction velocity, were significantly improved vs wait list<br>Tibial nerve NCS no significant difference<br>Acup superior to wait list in |

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| | | | | improvement of burning pain, cramps, numbness, frequency of symptoms and unsteadiness of gait |
| Ben-Arye et al 2022[35] | CIPN<br>Mixed cancer types (breast, gynae, blood)<br>Mixed chemo agents | **RCT -** Prospective, pragmatic, patient-preference study<br>Acupuncture plus usual care vs acupuncture and integrative oncology (randomised) plus usual care vs usual care alone during active chemo<br>Twice weekly acupuncture for 6 weeks | n = 168<br>69:67:32 | Both intervention arms (vs controls) improved on:<br>FACT-Tax ($p$ = .038) and emotional well-being ($p$ = .04) scores;<br>FACT-TAX scores for hand numbness/tingling ($p$ = .007) and discomfort ($p$ < .0001); and EORTC physical functioning ($p$ = .045). Intervention groups A and B showed improved FACT-Tax physical well-being ($p$ < .001), FACT-TAX total score ($p$ < .001), FACT-TAX feet discomfort ($p$ = .003), and EORTC pain<br>Assessed at 6 weeks and 9 weeks |
| Chan et al 2022[34] | CIPN (oxaliplatin)<br>Colorectal cancer | **RCT -** Sham-controlled single-blinded randomised trial<br>EA vs sham during active chemo<br><br>EA weekly for 12 weeks with 12 weeks follow-up | n = 60<br>30:30 | EA group exhibited significant alleviation of CIPN severity during chemotherapy vs Sham. EA also improved the physical function, role function, and social function of CRC patients. No significant differences in tests of vibration or light touch sensation. EA appeared to be a safe treatment for CIPN and was both feasible and acceptable to CRC patients during chemotherapy |
| Dietzel et al 2023[65] | DPN | **RCT**<br>Manual acupuncture vs waitlist<br>12 treatments over 8 weeks | n = 62<br>31:31 | Primary: VAS for overall complaints<br>Secondary: VAS pain, neuropathic pain symptom inventory (NPSI), emotional dimensions of pain, SF-12, and diabetic peripheral neuropathic pain impact (DPNPI)<br>Acupuncture leads to significant and lasting reductions in DPN-related complaints<br>compared to routine care and is well tolerated with minor side effects. |
| Hoerder et al 2023[12] | DPN | **RCT**<br>Manual acupuncture plus usual care vs waitlist plus usual care<br>12 treatments over 8 weeks | n = 62<br>31:31 | Outcome parameters were evaluated after 8, 16 and 24 wk and included neurological scores, such as an 11-point numeric rating<br>scale (NRS) 11 for hypesthesia, neuropathic pain symptom inventory (NPSI),<br>neuropathy deficit score (NDS), neuropathy symptom score |

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| | | | | (NSS); nerve conduction studies (NCS)<br>Acupuncture may be beneficial in type 2 diabetic DPN and seems to lead to a reductionin neurological deficits. No serious adverse events were recorded. |
| Ben-Arye et al 2023[66] | CIPN (taxane)<br>Gynae & breast cancer (taxane) or blood cancers (neurotoxic chemotherapy agents) | **RCT (multicenter)**<br>Acupuncture plus usual care (Group A) vs acupuncture and integrative oncology plus usual care (Group B) during active chemo<br>Twice weekly acupuncture for 6 weeks | n = 120<br>60:60 | Baseline to 6-week improved scores were similar in both groups for FACT-Tax physical wellbeing and hand numbness/tingling, EORTC physical functioning and global health status and MYCaW scores. FACT-tax scores for foot numbness/tingling improved only in Group A, while FACT-tax emotional wellbeing and EORTC pain scores improved only in Group B. Group B showed greater improvement than Group A in FACT-tax neuropathy-related concerns at 24 hours and 7 days after the first treatment. |
| Huang et al 2023[32] | CIPN (colorectal cancer -stage III) prevention of CIPN (oxaliplatin) | **RCT** Acup vs sham (Streitberger on same points as verum) 30 minutes retention; twice weekly during chemo cycles<br>84.6% of participants received at least 8<br>cycles of chemotherapy (range 5-12) | n = 32<br>16:16 | Primary: NCV and Von Frey touch sensitivity tests on fingers and toes<br>Secondary: (FACT-G), FACT/GOG-Ntx subscale and (BPI-SF)<br>Acup: no change in NCV or touch sensitivity, sustained at 6 months follow-up<br>Sham: Significant reductions in motor NCV and touch sensitivity<br>Acup exerts a neuroprotective effect which lasts for at least 6 months |
| **Systematic Reviews and Other Reviews** | | | | |
| **Study** | **Condition** | **Study type** | **Number of subjects** | **Outcomes** |
| Chen et al 2013[67] | DPN | **SR of manual acup RCTs**<br>25 trials all published in Chinese journals | n = 1,649 | Despite the number of trials of manual acupuncture for DPN and their uniformly positive results, no clinically relevant conclusions can be drawn from this review due to the trials' high risks of bias and the possibility of publication bias. |
| Brami et al 2016[68] | CIPN | **SR of natural products and complementary therapies for CIPN**<br>Only acup study is Rostock (EA) | | |
| Dimitrova et al 2017[69] | PN associated with diabetes, Bell's palsy, carpal tunnel syndrome, HIV, | **SR & MA of acup for PN**<br>15 studies :13 RCTs, a long-term follow-up, and a re-analysis of a prior RCT | | The majority of RCTs showed benefit for acupuncture over control in the treatment of diabetic neuropathy, Bell's palsy, |

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| | and idiopathic. | | | and carpal tunnel syndrome. Acupuncture is probably effective in the treatment of HIV-related neuropathy, and there is insufficient evidence for its benefits in idiopathic neuropathy. Acupuncture appears to improve nerve conduction study parameters in both sensory and motor nerves. |
| Li et al 2019[25] | CIPN (breast cancer and multiple myelomas with mixed chemo types) | **SR** (3 RCTs)<br>Han 2017 – manual acup<br>Lu 2017 - manual acup<br>Rostock 2013 - EA | | 2 studies (Han & Lu) found acup effective in reducing CIPN pain and QoL<br>1 study (Rostock) found no benefit in reducing CIPN pain, symptoms or QoL |
| Chien et al 2019[26] | CIPN (All cancers including breast cancer and multiple myelomas with mixed chemo types) | **SR & MA** (6 RCTs) High quality on modified Jadad scale | n = 386 | Significant improvements in pain scores and nervous system symptoms based on Functional Assessment of Cancer Therapy/Neurotoxicity questionnaire scores. No significant change in nerve conduction velocity. |
| Nash et al 2019[14] | DPN | **SR** of acup 10 studies:<br>3 RCTs, 2 pilot RCTs, 3 uncontrolled clinical trials, 1 quasi-RCT and 1 prospective case series. | n = 432 | Acupuncture for DPN appears to improve symptoms. However, the application of acupuncture varies greatly, and the quality of included studies was generally low. Available studies have varyng methodologies and different outcome measures. Further, suitably powered studies using appropriate DPN outcome measures are required. |
| Hwang et al 2020[36] | CIPN | **SR & MA** (13 RCTs: 9 acup; 4 EA)<br>10 from China not accessible<br>Only 3 available: Rostock, Greenlee and Han 2017 | n = 832 | 5 RCTs showed that acupuncture was more effective than pharmaceutical treatment in terms of efficacy rate. The quality of included studies was poor. |
| Jin et al 2020[39] | CIPN | **SR** 19 RCTs | n = 1,174 | The results showed that acupuncture significantly increased the effective rate of CIPN compared with medicine and sham acupuncture. And acupuncture had a good effect on the recovery of nerve conduction velocity and improving pain. |
| Yu et al 2021[15] | DPN | **Review of 18 SRs (112 RCTs)**<br>13 SRs in Chinese, 5 in English<br>3 SRs published “overseas” (outside China) | n = 8,378 | Acupuncture appears to have an effect on DPN, effectively improving nerve conduction and clinical symptoms. Methodological quality of included studies, assessed with |

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| | | | | AMSTAR2 and PRISMA, was generally very low.<br>Clinical effectiveness (112 RCTs – 8,378 subjects): Overall acupuncture was effective in treating DPN across 13 items<br>Median nerve sensory conduction velocity (31 RCTs – 2,142 subjects): Overall acupuncture was effective across 9 items<br>Median nerve motor conduction velocity (34 RCTs – 2,355 subjects): Overall acupuncture was effective across 10 items<br>Common peroneal nerve sensory conduction velocity (32 RCTs – 2,241 subjects): Overall acupuncture was effective across 11 items<br>Common peroneal nerve sensory conduction velocity (36 RCTs – 2,338 subjects): Overall acupuncture was effective across 12 items |
| Cho et al 2021[16] | DPN | **Narrative review:** 10 human: 1 EA (Shin 2018), 8 manual acup, 1 manual acup + laser<br>5 animal: 4 EA, 1 manual acup<br><br>Acup mediated through various molecules present in the peripheral nerves and spinal cord, such as P65, GPR78, and TRPV1 | | Furthermore, in all studies, acupuncture was applied for more than 20 min. This may be due to the report that acupuncture applied 20–30 min resulted in longer-lasting outcomes |
| Lin et al 2021[13] | DPN | **Review of 18 SRs,** 15 from China 3 published in West: Nash, Chen and Dimitrova | | |
| Zhao et al 2021[37] | CIPN<br>Paclitaxel | **A review of clinical and basic studies:**<br>**Effectiveness** - 8 RCTs: 5 manual acupuncture, 1 EA, 1 EA plus manual acupuncture, 1 manual acupuncture plus reflexology<br>**Mechanism** – 9 studies: 6 rat studies; 3 mice studies<br>EA used for 7 studies, EA plus gabapentin for 1 study and bee venom acupuncture for 1 study | | 7 out of 8 RCTs showed improvement<br><br>Hyperalgesia alleviated in all 9 animal studies<br><br>Several peripheral and spinal neurotransmitters were identified including several cytokines such as ILs and TNFa. Receptors involved included cannabinoid, adrenal, NMDA and opioid receptors as well as TLRs and TRPV1. |
| Klafke et al 2023[70] | CIPN | **SR of Non-pharma interventions** for **prevention and treatment of CIPN**<br>Included 7 studies on acupuncture/acupressure for CIPN and 5 studies for cancer pain | | Mixed outcomes |
| Pei et al | CIPN | **SR** of 9 RCTs | n = 582 | In terms of pain relief and |

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| 2023[71] | | | | improved CIPN-specific quality of life, acupuncture plus standard care was better than standard care alone. In terms of pain relief, EA was more effective than usual care. Acupuncture may be effective and safe in the treatment of CIPN according to the analyzed studies. However, more studies with higher methodological quality are warranted in order to be able to draw firmer conclusions. |
| Shi et al 2023[43] | CIPN | **An umbrella review of the evidence to guide decision-making** in acupuncture therapies for CIPN<br>**9 SRs/MAs** including 28 RCTs | | Based on the existing evidence, acupuncture is effective and safe for patients with CIPN, as it can significantly improve effective rate, pain symptoms, quality of life, and nerve conduction velocity. However, given the low quality of current evidence, we should be cautious in interpreting this conclusion. |
| Zhang et al 2023[72] | CIPN | **A Network meta-analysis**<br>13 RCTs<br>Comparison of 6 acupuncture-related techniques (manual acupuncture, EA, EA + moxibustion, warm acupuncture, moxibustion, acupoint injection) and Western medicine. Western medicine treatments included vitamin B, mecobalamine, neurotropin, etc. The control group received Western medicine, sham or other treatments. | n = 746 | EA was superior to moxibustion, manual acupuncture, acupoint injection and Western medicine in improving the total effective rate of treatment of CIPN<br>EA + moxibustion was better than manual acupuncture, acupoint injection, and Western medicine.<br>Manual acupuncture's total effective rate was better than Western medicine.<br>EA was the most effective treatment for CIPN according to the surface under the cumulative ranking curve (SUCRA) ranking.<br><br>Ranked order of interventions: electroacupuncture, electroacupuncture + moxibustion, warm acupuncture, moxibustion, manual acupuncture, acupoint injection, Western medicine |
| McDonald et al 2023[73] | CIPN | **Narrative review** of EA for CIPN<br>7 studies: 5 described as pilot studies but all 7 had small sample sizes<br>3 studies on prevention (and treatment) of CIPN<br>4 studies on treatment of CIPN | n = 317 | Seven English-language trials using EA for preventing or treating CIPN were included. In 3 prevention studies, 1 had significant benefits, 1 had modest benefits, and 1 had worse pain in an EA group at follow-up, compared to sham controls. In 4 treatment studies, |

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| | | | | 2 had significant benefits, 1 had no difference from 3 controls, and 1 had sham control was superior to verum EA.<br>Most studies were limited by small sample sizes and some by suboptimal EA protocols.<br>It is inappropriate to say that EA is not recommended for CIPN prevention or treatment (as one very small pilot study suggested), because there is no robust evidence to justify this. Generally, research has found benefits and no harms. |
| **Other publications** | | | | |
| **Study** | **Condition** | **Study type** | **Number of subjects** | **Outcomes** |
| Deng et al 2013[74] | LU Cancer | **Evidence-based clinical practice guidelines** on Complementary Therapies and Integrative Medicine in Lung Cancer | | 2.5.3.2. In patients with cancer related pain and peripheral neuropathy, acupuncture is suggested as an adjunct treatment in patients with inadequate control of symptoms (Grade 2C) . |
| Chan et al 2022[34] | CIPN (colorectal cancer) | **Protocol** for single-blinded RCT | | |
| Chin et al 2023[75] | CIPN | **Protocol** for a NMA on efficacy and safety of different types of acup for CIPN | | |
| Wang et al 2020[76] | DSPN (diabetic distal systemic polyneuropathy) | **Protocol** for RCT – real vs sham acup | n = 210<br>105:105 | |
| Yu et al 2023[77] | DPN | **Bilbliometric study** | | |
| Gu et al 2023[44] | CIPN | **Data mining on acupoints used in CIPN trials**<br>24 trials: 20 positive, 4 negative | | |
| Dimitrova et al 2018[45] | PN | **Follow-up SR** focused on local acupoint selection | | |
| Zhang et al 2023[54] | Diabetes and depression | **Narrative review** on acupuncture's effects on increasing BDNF in diabetes (including DPN) and depression comorbidity | | In diabetes, acupuncture increases BDNF and other neurotrophins including NT-3 and insulin-like growth factor 1. |

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