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Introduction

In 2023, it is estimated that about 165,000 new cases of cancer were diagnosed in Australia and in 2020, almost 69,000 people received MBS-subsidised chemotherapy services (Australian Institute for Health and Welfare, 2023). Although cancer survivorship is rising, many survivors have poor Quality of Life (QoL) outcomes due to syndromes such as Chemotherapy Induced Peripheral Neuropathy (CIPN) (Zajaczkowska et al., 2019). The central nervous system is protected by the Brain Blood Barrier, unlike the peripheral nervous system which makes it susceptible to neurotoxic chemotherapy agents that accumulate and target different regions of the neuron (Schloss et al., 2013). The pathophysiological processes of CIPN may be multifactorial involving: oxidative stress; apoptotic mechanisms; altered calcium homeostasis; axon degeneration; membrane remodelling; immune processes, and neuroinflammation damaging nervous system structures (Schloss et al., 2013; Starobova & Vetter, 2017; Zajaczkowska et al., 2019). Unlike other cells in the body, nerve cells are not easily repaired or replaced once they are badly damaged (Park et al., 2020).

The main symptoms of CIPN are symmetric paraesthesia, hypoalgesia or hyperalgesia in a ‘glove and stocking’ distribution (Gu et al., 2020). Cancer patients who develop CIPN are three times more likely to fall (Lahans, 2007; Pei et al., 2023; Zajaczkowska et al., 2019). Affected hands can lose grasping ability and may not be able to discriminate between wet and dry materials. Patients complain of difficulties doing everyday activities such as exercise (Chien et al., 2019; Lagerstedt & Efverman, 2023; Lahans, 2007). CIPN may also have autonomous nervous involvement with symptoms such as diarrhoea, constipation, sweating, postural hypotension, laryngospasm, urogenital or sexual dysfunction (Gu et al., 2020; Pei et al., 2023). The prevalence of CIPN one month after finishing chemotherapy is around 68% see Table 2 (Colvin, 2019). Kandula’s study found that 48% of long-term survivors of childhood cancers had some evidence of neuropathy (Colvin, 2019; Kandula et al., 2018). In approximately one third of cases, it can be a permanent consequence of drug neurotoxicity (Schloss et al., 2013).

Debilitating CIPN symptoms can result in dose reductions of chemotherapy, non-compliance or stopping treatment which has implications for the efficacy of oncology treatment and survival (Colvin, 2019; Gu et al., 2020; Z. Li et al., 2019). The current literature mounts a global pursuit to improve standards for the assessment, prevention and treatment of CIPN (Chien et al., 2019)

Position Statement

Acupuncture is a front-runner in the race to find a safe treatment for CIPN, with distinct advantages over pharmacological and other non-pharmacological interventions. Firstly, acupuncture's mechanisms in neuromodulation and neuroendocrine adjustments are well studied (Chien et al., 2019) with pre-clinical trials suggesting the following acupuncture mechanisms have the potential to reduce CIPN symptoms: regenerating nerve fibres; nerve growth factor (NGF) and neurotropin-3 (NT-3) modulation in dorsal root ganglions (DRGs); suppressing the overexpression of TRPV1 involved in neuropathic pain, and to inhibit inflammatory pathways (Lu, 2020).

Acupuncture's unmatched safety record is supported by Shi's forest plot of the effective rate of the Cancer National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE). The Risk Ratio (RR) 0.51 (0.34, 0.77) favours the acupuncture intervention (Shi et al., 2023).

Acupuncture is widely used as an adjuvant therapy for treating the side effects of cancer treatment (Hwang et al., 2020) with acupuncture for CIPN potentially impacting a wide range of accompanying symptoms such as nausea, appetite change, drowsiness, dry mouth, hot flushes etc simultaneously (Jin et al., 2020).

The American Society of Clinical Oncologists and European Society for Medical Oncology clinical guidelines note that there is no recommended preventative agent and emphasise the importance of early cessation of neurotoxic chemotherapy prior to disabling symptoms, and there remains no FDA approved validated treatment for

preventing or reversing the condition of CIPN (Colvin, 2019; Hwang et al., 2020; K. Li et al., 2019).

Methodology

There continues to be a divergence between everyday clinician's evidence-based practice knowledge demands and research designed to demonstrate measurable biomedical outcomes. Clinicians use literature searches for clinical guidelines such as Lahan's 'Integrating Conventional and Chinese Medicine in Cancer Care: A Clinical Guide' (Lahans, 2007) and Zhang's 'An integrated clinical approach with Chinese Medicine Alleviating the side effects of cancer treatment' (Zhang et al., 2007) for insights into clinical reasoning. It's curious that the protocols in these textbooks of common clinical practice in China are rarely seen in clinical trials.

A library literature search was conducted for Systematic Reviews and Meta-Analysis (SR-MAs) using the key words 'chemotherapy induced peripheral neuropathy', 'systematic review', 'meta-analysis' and 'acupuncture' which identified Shi's Umbrella review of nine SR-MAs from 2018 to 2023 (Shi et al., 2023) see Table 3 and Kutcher's Integrative Review of 16 articles that include Quasi-experimental studies, retrospective chart reviews and case reports from 2011 to 2019 (Kutcher & LeBaron, 2022).

Umbrella reviews are 'reviews of reviews' involving the assessment of methodological quality, reporting quality, evidence quality of relevant SRs/MAs and re-analysis of the results. Shi followed the methodology of the PRIOR statement (Gates et al., 2022) for overviews of reviews of healthcare interventions and registered the review protocol with INPLASY.

Shi used AMSTAR2 (Shea et al., 2017) and Cochrane's GRADE to evaluate nine SR-MAs conducted from 2019-2023 which included 28 RCTs. The quality assessment of Shi's SR-MA's and Kutcher's studies rated low in both internal and external validity with serious acupuncture RCT methodological limitations including insufficient statistical power, high heterogeneity and biases. Only Xu's SR-MA was

rated of ‘moderate’ quality but involved only five trials (with 225 participants) and found that acupuncture and placebo acupuncture were not significantly different in reducing CIPN (Xu et al., 2022). The assessments identified systemic methodological weaknesses including imprecision in outcome measures, inadequate reporting of randomised allocation, lack of blinding, funding and publication biases (Shi et al., 2023). The ‘effective rate’ with poor measurement reliability and performance biases was used in five of Shi’s SR-MAs (Shi et al., 2023). The PN Grades of the participants are unknown, before or after the trials giving rise to further selection biases (Delgado-Rodríguez & Llorca, 2004). One of Kannan’s study’s frequency of treatment was 22-27 sessions per week, which is not feasible in private practice (Kannan et al., 2023; Rostock et al., 2013).

Sackett (2000) states that the RCT model removes the practitioner’s clinical judgement and meaningful patient values, which are central components of Evidence Based Medicine (Guyatt, 2008; Sackett, 2000; Thorpe et al., 2009). This is clearly seen in Kutcher’s Integrative Review which struggles with this incongruity in synthesising inconsistent outcome measures for evidencing a range of acupuncture protocols (Kutcher & LeBaron, 2022).

Discussion

Acupuncture and other CIPN treatments continue to be plagued by limited RCTs and confounding factors such as medications for other co-morbidities. This is shared across modalities as discussed in Hou’s SR (on pharmaceuticals, laser etc), Papadopoulou’s SR-MA on non-pharmacological Interventions (including yoga, exercise etc) and Kannan’s SR-MA on physiotherapy (Hou et al., 2018; Kannan et al., 2023; Papadopoulou et al., 2023). As an evidence-based practitioner community, clinicians need to have the confidence to push the importance of more meaningful patient centred outcomes such as QoL measures.

The ‘Powerful Placebo response’ is thought to be as high as 30% of all treatment effects for all therapies (Kaptchuk, 1998). Chien’s SR-MA of 6 RCTs involving 386 cancer patients showed that acupuncture has the potential to improve QoL in terms

of pain score and FACT-NTX assessment, yet no difference in Nerve Conduction Velocity (NCV) or relevant serum cytokines were reported. Kutcher's review also reported that patients who receive acupuncture generally report subjective improvement in symptoms of CIPN without improvement in objective measures (Kutcher & LeBaron, 2022). Papadopoulou's SR-MA of six RCTs with 349 participants on non-pharmaceutical interventions (NPIs) found although NPIs significantly reduced neuropathic pain, the effect on QoL was not supported (Papadopoulou et al., 2023).

The results from both Shi's and Kutcher's reviews are mainly favourable towards acupuncture (Kutcher & LeBaron, 2022). Shi's re-assessment indicated that acupuncture therapy had a significant favourable effect in outcomes including: Brief Pain Inventory (Short Form) (BPI-SF); Functional Assessment of Cancer Treatment - Neurotoxicity (FACT-NTX); Numerical Rating Scale for Pain Intensity (NRS); EORTC QLQ-C30 core QoL questionnaire; Motor Conduction Velocity (MCV); Sensory Conduction Velocity (SCV); Visual Analogue Scale (VAS) and NCI-CTCAE. Risk Ratio = 1.48 (1.31,1,67), I^2=46% (Shi et al., 2023). In Chien's SR-MA, RCTs were positive for acupuncture for bortezomib related neuropathy, negative for taxane and found no differences in objective measures such as proinflammatory cytokines. Jin's SR-MA of 19 RCTs with 1174 subjects found that the overall effectiveness of acupuncture was superior to neurotrophic drugs with the recovery of sensory function significantly better than the motor function after ten weeks of treatment (Jin et al., 2020).

Patient Population

Neurotoxicity is related to the accumulating dose of the chemo-regimen and type of chemotherapy drug see Table 4. There is also an important differentiation between patients who develop CIPN during treatment, one month or three months later (Hou et al., 2018). The timing of treatment entry whether the intervention was during chemotherapy or after chemotherapy is critical question to answer (Jin et al., 2020). The benefits of acupuncture appear to be more significant for patients with recent neuropathic symptoms (D'Alessandro et al., 2022). Most studies did not report

baseline data useful for sub-analysis including: participants base PN grade see Table 5, chemotherapy agent; dosage; treatment duration, or CIPN treatment entry, which is essential for any study's external validity and generalisability. None of the SR-MAs sub-analysed participant risk factors that can influence developing CIPN such as: older age; cardiovascular drugs; smoking; diabetes; diabetic neuropathy; alcohol; impaired renal function; decreased creatine clearance were reported on baseline (Colvin, 2019; Z. Li et al., 2019; Park et al., 2020; Zajaczkowska et al., 2019).

Intervention

The STRICTA guidelines are useful for insights into clinical reasoning, not all the included studies satisfied the STRICTA criteria, regrettably, many not providing any rationale or details of the acupuncture treatments (K. Li et al., 2019). TCM patterns for CIPN include: Heat damaging the Lungs and Body fluids; Damp Heat macerating the flesh; Stomach and Spleen deficiency; Liver and Kidney Deficiency (Kutcher & LeBaron, 2022; Lahans, 2007) or blood stasis patterns (Z. Li et al., 2019). Zhang recommends treating severe numbness with ST40, BL17, CV17 and local acupoints using the reducing method, and a needle retention time of 30 minutes (Zhang et al., 2007). Lahan's recommends points carrying the strongest Yang Qi on the affected channels, especially on the Yangming and Shaoyang channels to treat Wei Suo and Wei Bi Syndromes (Lahans, 2007). Most of the RCTs reported using Yangming and local points such as Ba Feng and Ba Xie in line with TCM treatment strategies for Wei Syndrome (Chien et al., 2019; Jin et al., 2020; K. Li et al., 2019; Liu et al., 2021; Pei et al., 2023; Shi et al., 2023).

Findings for electro-acupuncture (EA) were contradictory. Zhang's RCT found EA superior to manual acupuncture (MA) in terms of symptom relief (Chien et al., 2019) whereas Li's SR found that MA showed positive effect while EA lacked benefit (K. Li et al., 2019). Greenlee's study found that EA worsened neuropathic pain during their chemotherapy (Greenlee et al., 2016). The strong stimulation of EA may aggravate the pain, therefore EA may not be as effective and safe as MA for CIPN (Jin et al., 2020).

Comparators

The evidence for sham acupuncture as an effective placebo is controversial, Grillo's (2018) study found that 'De Qi' could be felt in the sham needling (Chae et al., 2018; Grillo et al., 2018; Lee et al., 2011; Xie et al., 2013). Unsurprisingly, Xu's SR-MA found no significant difference between true acupuncture and placebo acupuncture (Xu et al., 2022).

The most promising pharmacological treatment so far is the anti-depressant Duloxetine, with the therapeutic effect modest. It was not tolerated by some patients who experienced adverse effects of nausea and drowsiness and there were polypharmacy interactions with other medications commonly prescribed in cancer due to multimorbidity (Crichton et al., 2022; K. Li et al., 2019; Pei et al., 2023). Clinical trials for Vitamin E, fish oil, Vitamin B, glutamines, glutathione, alpha lipoic acid, N-acetylcysteine, oxcarbazepine and xaliproden, intravenous calcium/magnesium show some promise, although convincing evidence for their efficacy remains lacking (Chien et al., 2019)

Both Hwang's and Pei's SR-MA's support acupuncture's efficacy over Vitamin B. Pei's SR-MAs of 9 RCTs involving 582 patients results found that acupuncture may generate a better effect on sensory neuropathic pain than Vitamin B, the efficacy of EA plus glutathione (GSH) appeared to be better than GSH alone in alleviating sensory neurotoxicity and improving Nerve Conduction Velocity (NCV) and acupuncture plus methylcobalamin showed more favourable results than methylcobalamin alone in relieving neuralgia, restoring NCV and improving QoL. In terms of CIPN specific QoL, acupuncture plus standard care was better than standard care alone and in terms of pain relief, EA was more effective than usual care. Hwang's SR-MA of 12 RCTs involving 832 participants found acupuncture was found to be more effective than Vitamin B in terms of clinical efficacy rate (Hwang et al., 2020).

Outcomes

There remains no consensus gold standard for the clinical assessment of CIPN (McCrary et al., 2017). The PN grades from CTCAE require no diagnostic tests e.g. neuro-imaging, functional testing or nerve conduction studies, although a Grade 1 reduction in PN was considered effective (eviQ, 2017) subjectivity is problematic as a reliable outcome measurement (Colvin, 2019).

More understanding of the mechanisms of chemotherapeutic agents and CIPN will assist identifying future biomarkers such as cytokines and neurotrophic factors. Hwang's SR-MA reported that acupuncture improved NCV, lasting for one month (Hwang et al., 2020) however, nerve conduction tests may not correlate with pain (Baviera et al., 2019).

Shi's outcomes used validated measures: Patient Neurotoxicity Questionnaire (PNQ) (Tsoleridis et al., 2021); NCV (Mallik & Weir, 2005); FACT-NTX (Cheng et al., 2020); NRS; VAS; BPI-SF, and NCI-CTCAE. A Grade 1 reduction in PN was considered effective (eviQ, 2017). Jin's SR-MA used a 'total effective rate' of nimodipine scoring – grading peripheral neurotoxicity (Jin et al., 2020).

Conclusion

Although Shi's and Kutcher's reviews generally favour acupuncture, the results remain unconvincing due to problematic methodological weaknesses previously discussed. Safe and effective therapies are urgently needed for this considerable unsolved challenge for cancer patients and oncologists (K. Li et al., 2019; Pei et al., 2023). Considering the safety and lack of serious adverse effects associated with acupuncture and a lack of definite treatment for CIPN, acupuncture should be considered for treating CIPN (Chien et al., 2019). Jin recommends future studies comparing acupuncture to Duloxetine (Jin et al., 2020). The search for CIPN treatments involves developing our understanding of the pharmacology of chemotherapeutic agents and the mechanisms of CIPN, and further work on improving diagnostic tests for assessment guidelines to determine validated outcome

measures for trials. Large scale and long term RCTs are required as none of the included RCTs reached significant statistical power. The quality of reporting on the STRICTA guidelines needs to improve with researchers publishing rationale and treatment strategies. Future acupuncture RCT's should improve both patient and treatment sub-analyses by including data on chemotherapy agent, dosage and regimen, treatment entry points and long term follow ups.

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Appendices

Table 1 Glossary

Abbreviation	Description
AMSTAR2	A MeaSurement Tool to Assess systematic Reviews
ASCO	American Society of Clinical Oncologists
BPI-SF	Brief Pain Index – Short Form
CIPN	Chemotherapy-induced Peripheral Neuropathy
CWM	Conventional Western Medicine
DGR	Dorsal Ganglion Root
EA	Electro-acupuncture
EBM	Evidence Based Medicine
EORTC QLQ-C30	Core Quality of Life questionnaire is designed to measure cancer patients' physical, psychological and social functions
FACT-NTX	Functional Assessment of Cancer Therapy - Neurotoxicity
FDA	Food and Drug Administration – US Federal Agency
GRADE	a systematic approach to rating the certainty of evidence in systematic reviews and other evidence syntheses
GSH	Glutathione
I^2	Heterogeneity measure in meta-analysis
INPLASY	International Platform of Registered Systematic Review and Meta-analysis Protocols
MA(s)	Meta-analysis

Abbreviation	Description
MCV	Motor Conduction Velocity
MYCaW	Measure Yourself Concerns and Well-being cancer-care questionnaire
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for. Adverse Events
NCV	Nerve Conduction Velocity
NGF	nerve growth factor
NRS	Numeric Rating Scale for Pain Intensity
NT-3	Neurotropin-3
PICO	Population, Intervention, Comparator, Outcomes elements in RCTs
PN	Peripheral Neuropathy
PRIOR	Reporting guideline for overviews of reviews of healthcare interventions
PSQI	Pittsburgh Sleep Quality Index
RCT(s)	Randomised Control Trials
RR	Risk Ratio
SCV	Sensory Conduction Velocity
SR(s)	Systematic Review(s)
STRICTA	STandards for Reporting Interventions in Clinical Trials of Acupuncture
TCM	Traditional Chinese Medicine
TRPV1	Transient receptor potential vanilloid 1
VAS	Visual Analogue Scale

Table 2: Chemotherapies comparisons of Incidence/Prevalence

(Colvin, 2019)

Chemotherapy	Approx Incidence/Prevalence CIPN
Oxaliplatin	Acute: 85%-965, chronic: 40%-93%
Cisplatin	12%-85%
Paclitaxel	61%-92%
Bortezomib	47%
Vincristine	20%
Combined cisplatin and paclitaxel	69%-76%

Table 3: Umbrella Review Summary of SR-MAs

(Shi et al., 2023)

Lead Author	Year	Title	Trials	Subjects
Chien (Chien et al., 2019)	2023	The Efficacy of Acupuncture in Chemotherapy-Induced Peripheral Neuropathy: Systematic Review and Meta-Analysis	6	386
Papadopoulou (Papadopoulou et al., 2023)	2023	Non-pharmacological Interventions on Pain and Quality of Life in Chemotherapy Induced Polyneuropathy: Systematic Review and Meta-Analysis	6	349

Lead Author	Year	Title	Trials	Subjects
Kannan (Kannan et al., 2023)	2023	Physiotherapy interventions for pain relief in individuals with peripheral neuropathic pain: A systematic review and meta-analyses of randomized controlled trials	4	253
Pei (Pei et al., 2023)	2022	The effectiveness and safety of acupuncture / electroacupuncture for chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis	9	582
Xu (Xu et al., 2022)	2022	The effectiveness and safety of acupuncture for chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis	5	225
Liu (Liu et al., 2021)	2021	Systematic evaluation and meta analysis of acupuncture for chemotherapy-related peripheral neuropathy	18	904
Jin (Jin et al., 2020)	2020	Efficacy and Safety of Acupuncture against Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis	19	1174
Hwang (Hwang et al., 2020)	2020	A systematic review and meta-analysis of the efficacy of acupuncture and electroacupuncture against chemotherapy-induced peripheral neuropathy	13	832
Yan (Yan et al., 2018)	2018	Meta-analysis of clinical study of acupuncture for chemotherapy-induced peripheral neuropathy	6	417

Table 4: Pathomechanisms of Chemotherapy Drugs

Drug	Pathomechanisms
Taxanes	tubulin inhibitors that disrupt the microtubule structure, leading to impairment of the axoplasmic transport and dying back neuropathy (Chien et al., 2019)
Bortezomib	damages the dorsal root ganglia neuronal cell bodies, leading to peripheral nerve degeneration (Chien et al., 2019)
Platinum analogs	accumulate in the dorsal root ganglion cell bodies of sensory nerves, reducing nuclear size and damage DNA (Chien et al., 2019; Shi et al., 2023; Xu et al., 2022)

Table 5: Peripheral Neuropathy Grades

(eviQ, 2017)

Grade 1	asymptomatic
Grade 2	moderate symptoms; limiting instrumental activities of daily living
Grade 3	severe symptoms; limiting self-care activities of daily living
Grade 4:	life threatening consequences; urgent intervention indicated