ARE ACTIVE INTERVENTIONS EFFECTIVE COMPARED TO PASSIVE NON-PHARMACOLOGICAL INTERVENTIONS IN THE TREATMENT OF SENSORY AND MOTOR SYMPTOMS AND IMPROVING QUALITY OF LIFE IN PATIENTS DIAGNOSED WITH CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY?

LITERATURE REVIEW

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Preface

The following literature review was written as part of the International Physiotherapy Program at the Hanze University of Applied Sciences acting as the final graduation product. It is going to investigate the effect of active interventions such as exercise therapy as well as passive non-pharmacologic interventions such as acupuncture, electroacupuncture, or cryotherapy on patients diagnosed with chemotherapy-induced peripheral neuropathy. This topic was chosen based on personal experience during internships and personal interest in the field of neurology. The first time I encountered the neurologic problems chemotherapy can result in, was when one of my family members needed to undergo chemotherapy. During an internship, I again saw patients that did undergo chemotherapeutic treatment experiencing CIPN, which sparked my interest in the topic and as I started researching it, I realized that the topic has gathered attention from researchers only over the last ten years. With the thesis, I had the opportunity to look into a topic that was not covered over the previous course of the study program. Next to that, it allowed for me to combine my topic of interest with the personal experience I had. With the review I hope that it gives further insight into the treatment of CIPN and draws light to the topic. As it is also comparing two types of interventions to each other, I also hope to spark a discussion on the topic and probably lead to further research.
Lastly, I would like to thank my tutor Caspar Mijlius, who provided feedback and guidance throughout the process of writing this thesis.

Abstract

Introduction: Cancer was diagnosed in 19.292.789 patients worldwide in 2020, depending on the type of cancer treatment may involve chemotherapy. If a neurotoxic agent is used, patients can develop chemotherapy-induced peripheral neuropathy (CIPN) affecting 68% of patients within the first months of treatment. CIPN involves sensory, motor or autonomic symptoms. As there is currently no treatment, most often during chemotherapy the dosage needs to be reduced which may have a negative effect on the survival rate of patients. The American Society of Clinical Oncology (ASCO) only recommend the usage of duloxetine to treat painful CIPN symptoms, nonetheless studies having found positive outcomes with exercise therapy, acupuncture or whole-body vibration. As there are no recommendations made, this review is aimed to answer the question whether active interventions or passive non-pharmacological interventions are more effective in the treatment of CIPN symptoms and decreased Quality of Life in patients diagnosed with CIPN.

Method: The literature search was conducted on three different platforms: PubMed, CINHAL, and SpringerLink. RCTs that investigated the effect of either passive non-pharmacologic or active intervention, not a mixture of both, on objective and/or patient reported CIPN symptoms and Quality of Life (QoL), written in English and not recruiting patients below the age of 18 years were included. Quality assessment of the studies was done using the PEDro scale, while data synthesis was done using the Best Evidence Synthesis method.

Results: After completing literature research, ten studies were included in the review, four studies used active interventions, with the remaining six investigating various passive interventions. Quality assessment showed that eight studies were of “good” quality with two studies being rated “fair” quality. Strong evidence was found for active interventions all consisting of sensorimotor, endurance, and resistance training having a positive effect on CIPN symptoms. There was limited evidence that these interventions had a positive effect on QoL. Individual studies passive non-pharmacologic interventions found significant improvements in CIPN symptoms and QoL, however combined they only display limited evidence for having a positive effect on CIPN symptoms and QoL.

Conclusion: This review shows that there is an indication that active interventions are more effective in the treatment of CIPN symptoms compared to passive non-pharmacologic interventions according to current evidence. It remains unclear whether one is more effective in the treatment of decreased QoL, as evidence was limited for both intervention types.

Table of content

Introduction

The World Health Organization (WHO) estimated that in 2018 there were 9.6 million deaths that can be attributed to cancer, making it the second most common cause for mortality in that year.(World Health Organization, 2018)
In 2020 the most common forms of cancer were breast and lung cancer; it was estimated that there were 2.261.419 new cases of breast and 2.206.771 new cases of lung cancer worldwide.(World Health Organization, 2020) Treatment of cancer can involve chemotherapy aimed at reducing the size of the tumor, how cancer is treated depends on the type of cancer.(World Health Organization, 2018) When treated with neurotoxic agents, a common side effect is chemotherapy-induced peripheral neuropathy (CIPN), medications based on the following agents are associated with causing CIPN: platinums, vinca alkaloids, taxanes, and proteasome inhibitors. It is thought that approximately 68% of patients that receive chemotherapy with a neurotoxic agent develop CIPN within the first month of treatment, with 20-30% of patients developing a chronic form that may persist for 6 months or longer.(Licht et al., 2021)

CIPN most often leads to sensory symptoms like burning, numbness, tingling, loss of sense for vibration, (cold) allodynia, and hyperalgesia.(Licht et al., 2021; Staff et al., 2017) Additionally, it can also involve the motor and autonomous nervous system causing muscle weakness, cramps, trouble with fine motor tasks, dysregulation of heartbeat, blood pressure, intestinal peristalsis, and urinary or erectile dysfunction.(Licht et al., 2021; Staff et al., 2017) This can affect a patient's quality of life (QoL) and increase their risk of falling, as they might develop balance problems.(Flatters et al., 2017)

There is no pharmacologic or non-pharmacologic treatment intervention that has been shown to be able prevent or treat CIPN. The American Society of Clinical Oncology (ASCO) published a guideline in 2020 in which they concluded that the only treatment they can recommend is the medication duloxetine that acts on the painful symptoms of CIPN. Non-pharmacologic interventions like exercise therapy, acupuncture, or cryotherapy showed too little evidence for the ASCO to make recommendations on their prescription to CIPN patients. (Loprinzi et al., 2020) However, there are results from recent studies that exercise therapy is effective in the treatment of CIPN symptoms in patients with various types of cancer and chemotherapeutic agents used.(Bland et al., 2019; Duregon et al., 2018) Next to active interventions, there are also indications that non-pharmacologic interventions such as whole-body vibration or acupuncture may be effective in the treatment and prevention of CIPN.(Hwang et al., 2020; Streckmann et al., 2019) This shows that there are two types of interventions that have been shown to be effective, however not all studies are high quality and they have not been compared before.

To the knowledge of the researcher there has been no systematic review conducted comparing multiple non-pharmacological treatment interventions, however for therapists encountering patients suffering from CIPN this could aid them in the clinical decision-making process. Which is why the following systematic review is aimed to answer the question, if active interventions are more effective compared to passive non-pharmacologic interventions in the treatment of CIPN symptoms and a decreased QoL in patients diagnosed with CIPN. As lack of high-quality evidence was one of the reasons for the ASCO to not make any recommendations (Loprinzi et al., 2020), therefore a secondary aim of this review is going to be investigating the most common source of bias in the included studies.

Method

Literature search

The study selection was done according to the PRISMA guideline (Moher et al., 2009), which involves the following steps: identification, screening, eligibility, and inclusion. The platforms PubMed, SpringerLink, and CINHAL were searched for relevant studies in the period from the 22.02.2021 till the 17.03.2021. The following MeSH terms and search terms were used and combined using the Boolean operators to limit or broaden search results:

“CIPN”, “chemotherapy-induced peripheral neuropathy”, “treatment”, “rehabilitation”, “quality of life”, “cancer”

Platform	Final search string
CINHAL	CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment"
PubMed	CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" AND “quality of life” AND “cancer”
SpringerLink	CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" AND “quality of life”

The full search string per platform is displayed in Appendix 1.

Study selection

The abstract and titles of the studies resulting from the literature search were initially screened individually by the researcher. The titles and abstract that were found to be relevant for the review were then screened full text. Inclusion criteria were outcomes focused on CIPN symptoms and QoL, interventions that required only active or passive participation, and study designs that involved randomizations and control. Studies were excluded if patients were younger than 18 years of age, treatment interventions involving CIPN aimed medication, or if the data was not presented for all the investigated outcomes. For this systematic review “active interventions” are going to be defined as treatment interventions that do not involve medication for CIPN symptoms during which the patients actively participated. “Passive non-pharmacologic interventions” are going to be defined as treatment interventions that do not involve medication, but have the intervention performed on the patient. After confirming full text articles were meeting the set eligibility criteria, studies were included in the review.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Population	Cancer patients, undergoing or having undergone chemotherapy, diagnosed with CIPN
	Intervention	Fully passive interventions Fully active interventions
	Outcome measurement	Patient reported CIPN symptoms, objective CIPN symptoms, pain, QoL
	Study design	Randomized, controlled trial; randomized, controlled pilot trial
Exclusion criteria		Animal studies, other language than English, only QoL or CIPN related measurements, only abstract available, 2011 or earlier

Quality assessment

After the literature research was conducted the researcher assessed the included articles for risk of bias. The RCTs were assessed using the PEDro scale (*PEDro Scale - PEDro*, 1999). This scale rates the risk of bias of RCTs by looking at 11 different criteria, producing a score ranging from 0 to 11. The numeric score can be translated to words, with "excellent" translating to 10-9 points, "good" translating to 8-6 points, "fair" translating to 5-4 points, and 3-0 points translating to "poor" (Cashin & McAuley, 2020).

Data extraction

From the included articles the following data points were extracted by the researcher: author, publishing year, population, intervention, control, measurement tool, and outcomes. The outcomes were then further grouped whether they were concerning QoL, patient reported or objective CIPN symptoms for analysis.

Data synthesis

There was no manipulation performed on the extracted statistical data, as Best Evidence Synthesis according to Kennedy et al. was chosen, the criteria can be seen in Table 2. If a study was high, moderate quality was based on the PEDro rating, with "good" and "excellent" being defined as high quality, while moderate quality corresponded to the "moderate" rating. Outcomes are going to be defined as significant when there is a p-value ≤0.05, next to the p-value Means, Standard Deviations (SD) and effect sizes are going to be extracted from the RCTs.

Table 2 Criteria for Best Evidence synthesis

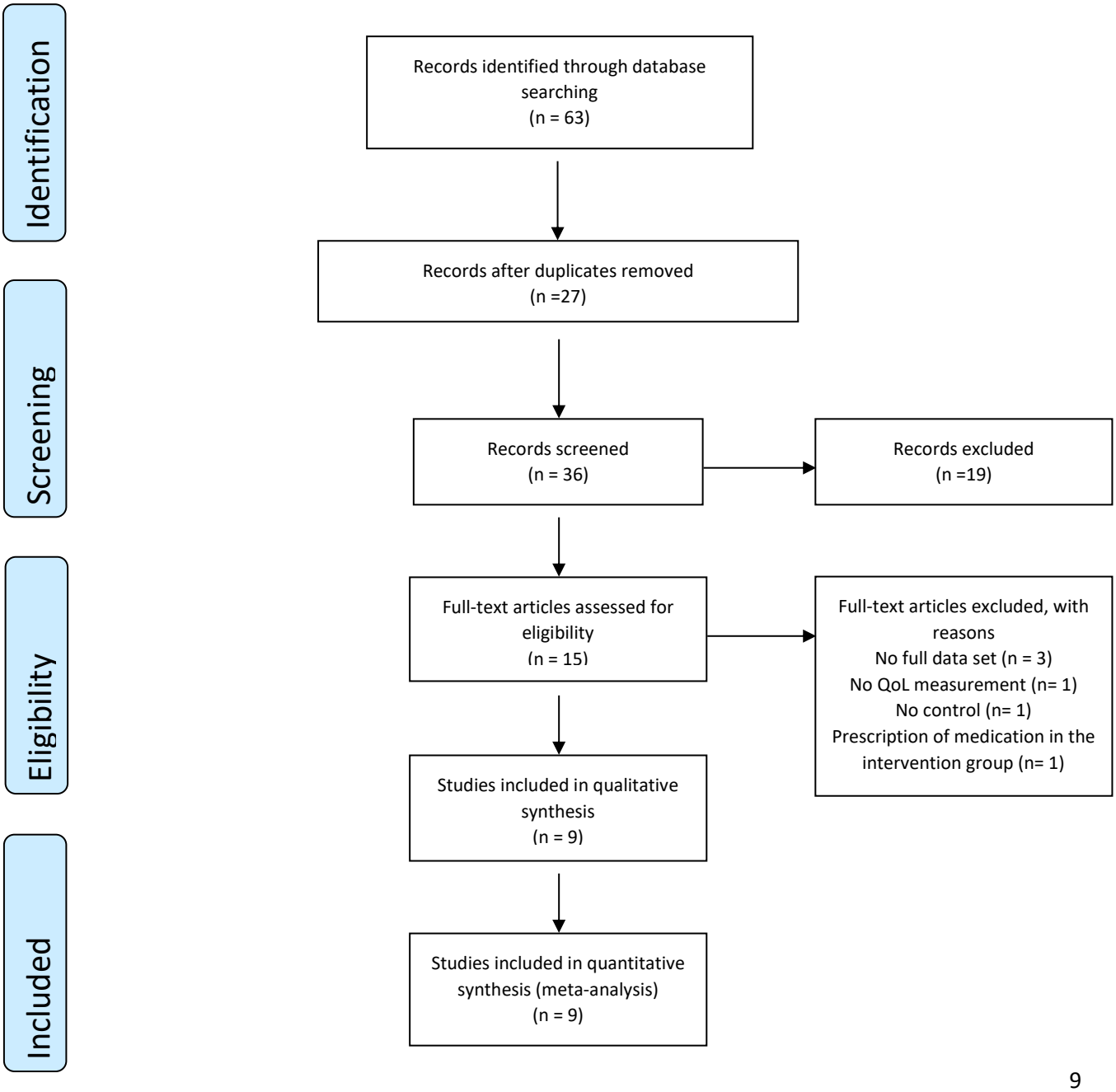
Level of evidence	Minimum quality	Minimum quantity	Consistency	Terminology
Strong	High (>85%)	Three	Three high quality studies agree If more than three articles, 3/4th of the medium to high quality studies agree	Recommendation
Moderate	Medium (85%-50%)	Two high quality studies OR Two medium quality studies and one high quality study	Two high quality studies agree OR Two medium quality studies and one high quality study agree If more than three studies, more than 2/3rd of the medium and high-quality studies agree	Practice considerations
Limited	Medium (85%-50%)	One high quality OR Two medium quality OR One medium quality and one high quality study	If two articles (high and/or medium quality) agree OR If more than two studies, more than ½ of the medium and high-quality studies agree	
Mixed	Medium and high	Two	Findings from medium and high-quality studies are contradictory	
Insufficient	No high-quality study studies, only one medium quality study, and/or any number of low-quality studies			

Results

Included articles

The final search string per platform led to a total of 504 results, with 63 results on PubMed, 326 results on SpringerLink, and 115 hits on CINHAL. Out of which 59 titles were selected for further screening based on inclusion and exclusion criteria. After removing duplicates 34 abstracts were then screened, resulting in the exclusion of 19 articles, with the remaining 15 studies were screened full text to check for their eligibility. Three studies were being excluded for not giving full data on all outcome measures used. Another three studies were excluded for not having a QoL measurement, a control group, and for prescribing medication aimed to reduce CIPN symptoms respectively. After checking for eligibility, 10 articles were included in the final review. This process is displayed in Figure 1 below.

Figure 1 PRISMA flowchart according to Moher et al. (2009)



Quality assessment

Quality analysis of the included studies showed that there were two RCTs with fair quality scoring 5/10, while the other eight RCTs were of good quality, mostly scoring 6/10 with one study by Son et al. scoring 8/10. The most common criteria that wasn't met by the studies was the blinding of therapists, which was only done in one out of the nine studies included. The following criteria were each only met twice: blinding of the subjects, blinding of the assessor and completion of therapy of at least 85% for one key outcome. While the criteria met that were fulfilled in all the studies included: giving eligibility criteria, randomization, similar baseline characteristics, between-group analysis, giving point and variability measures, and the intention-to treat analysis. The exact scoring per article can be viewed in Appendix 2.

Population

All studies combined there were 548 participants. The most common type of cancer diagnosed was breast cancer (n=240), followed by 74 participants diagnosed with colorectal cancer. Out of all participants the majority were female (n=327) with 111 participants being male. The reported mean age ranged from 44 to 70 years in all studies. When reported the most common type of chemotherapeutic agent used was Taxane, with four of the studies including solely participants treated with a Taxane type agent and two including participants treated with various chemotherapeutic agents. Five studies recruited female breast cancer patients exclusively, while one study included only patients diagnosed with colorectal cancer of both genders. The remaining RCTs did not specify which chemotherapeutic agent was used and/or did not include one cancer type exclusively.

Intervention

Of the articles included, five RCTs involved passive interventions, with four of the included articles looking into active interventions. The majority of passive interventions investigated electroacupuncture, while one study looked into cryotherapy, and another study used acupuncture. The four RCTs that had participants perform active interventions all involved aerobic endurance training, resistance training, and balance exercises. Control interventions for the active interventions varied per study, one used delayed exercise compared to the IG, one did not include balance exercises compared to the IG, one standard care, and another had no intervention carried out for control. In the passive non-pharmacologic interventions control interventions consisted of sham-devices in one study, usual care in another two RCTs, no intervention in one study, and of hydroelectric baths, Vitamin B, and a placebo in another RCT.

Outcomes

The outcomes used for the CIPN symptoms varied between the studies, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN 20 item scale (EORCT-QLQ CIPN20) (Le-Rademacher et al., 2017) is the most frequent outcome used to present patient-reported symptoms of CIPN. The FACT-Neurotoxicity (FACT-Ntx) was used by 3 studies as well to have participants report on CIPN severity (Cheng et al., 2020), another questionnaire used was the Patient Neurotoxicity Questionnaire (PNQ) (Shimozuma et al., 2009). Objective CIPN symptoms were measured by the clinical version of the Total Neuropathy Score (TNSc) (Cavaletti et al., 2006), a numerical rating scale (NRS), the pinprick test (Lanting et al., 2020), a test for deep peripheral sensitivity disturbance using a tuning fork (Brown et al., 2017; Ridehalgh et al., 2018) , and a test battery involving tests for sensory symptoms, sensibility, strength, vibration threshold, and deep tendon reflexes. Five studies measured patient reported pain, three of them using the Brief Pain Inventory (BPI)(Tan et al., 2004) or it's short form (BPI-SF)(Mendoza et al., 2006). Quality of life was measured most often by the European Organization for Research and Treatment of Cancer Quality of

Life Questionnaire (EORTC-QLQ-C30)(Osoba et al., 1997), two studies used the FACT-G from the FACT-NTX to report QoL outcomes(Overcash et al., 2001). Solely one RCT used the FACT-Taxane (FACT-Tax) to report this outcome(D. Cella et al., 2003).

Best Evidence Synthesis

Active interventions

There is strong evidence that a combination of aerobic endurance training, resistance training, and balance training is effective in the reduction of sensory and motor CIPN symptoms. A combination of aerobic endurance training, resistance training, and balance exercises was used in four high quality RCTs, included into this review. Kneis et al. found that exercise had a positive effect on the sensory, motor, and autonomic CIPN symptoms as the EORTC-QLQ-CIPN dropped significantly in the IG by 10 points ($p< 0.007$), while it did not improve the QoL. Similar effects were found by Zimmer et al., who showed stable neurotoxicity scores compared to decreasing scores in the control group. While Streckmann et al. showed that the incidence of disturbance of deep peripheral sensitivity decreased significantly by seven participants in the IG group compared to zero in the CG ($p<0.001$) with increasing QoL scores by 12 points on the EORTC-QLQ-C30 ($p<0.013$). Bland et al. showed that there was no difference between early onset exercise and delayed exercise in CIPN symptoms, with both exercise interventions together showing significant improvements in sensory and motor symptoms at the last follow-up. QoL of life was improved in both groups.

Passive interventions

Electroacupuncture

The results showed that there is limited evidence that Electroacupuncture (EA) has a positive effect on symptoms of CIPN or QoL. Three studies investigated the effect of electroacupuncture (EA), Lu et al. found that there were positive effects on patient reported and objective CIPN symptoms as well as QoL, but the study was of only fair quality. Participants showed significantly increased EORTC-QLQ-C30 scores of 12 points ($p<0.03$) and significantly decreased PNQ motor score by one point ($p<0.01$)(Lu et al., 2020). Greenlee et al. found an increase in neuropathic pain, as well as the incidence of sensory symptoms compared to the CG ($p<0.03$), there were no effects on QoL or motor symptoms of CIPN. One RCT by Rostock et al found positive effects of EA on perceived severity of CIPN symptoms (-0.8 on NRS) and neuropathy score by one point decrease with no intergroup differences, both of the RCTs being of good quality.

Acupuncture

There's insufficient evidence for a positive effect of acupuncture on CIPN symptoms and QoL. Acupuncture was used in one good quality study, it's participants in the IG reported lower TNSc scores after eight weeks ($p<0.001$, effect size=0.42) and an increased neurotoxicity measured by the subscale of the FACT-Ntx ($p<0.003$, effect size=0.32) both with no significant intergroup difference. However, the FACT-G score increased significantly after eight weeks ($p<0.004$, effect size=0.42), again with no significant intergroup difference.

Cryotherapy

Ng et al. assessed the effect of cryotherapy during Taxane chemotherapy with moderate quality results, they found that it had a positive effect on QoL of life 9 months post-treatment ($\beta=10.69$, CI=1.5-19.88, $p<0.024$) and on motor symptoms 3 months post-treatment as 0% of participants in the IG scored a grade C or higher compared to 29,4% in control ($p<0.012$). However, they found no difference between groups at any other time point or change in CIPN symptom burden.

Table 3 – Data comparison

Researcher (year)	Design	Pedro score	Participants	Intervention group	Control group	Measurement	Results
Bland et al. (2019)	RCT	6/10	N=27 Mean age 50.2 Female Breast cancer Stage 1-3 Taxane neurotoxic agents	N=12 8-12 weeks 3 times/week Early Exercise Therapy	N=15 8-12 weeks 3 times/week Delayed exercise therapy	EORTC-QLQ-C30 EORTC-QLQ-CIPN20 Pinprick test Vibration sense with tuning fork	There was no significant change from baseline or difference between groups for all the EORTC-QLQ-CIPN20 subscales Overall QoL did only show significantly better score in the IG compared to CG pre-cycle 4 ($p<0.01$) Significantly less participants experienced impaired vibration sense in the IG group pre-cycle 4 ($p<0.01$)
Greenlee et al. (2016)	RCT	6/10	63 participants Mean age IG 51.8 CG 48.3 Female Breast cancer Stage 1-3 Taxane neurotoxic agents	N=32 12 weeks 2 times/week Electroacupuncture General acupoints: GB34, ST36, LI4, LI10 Lower Limb: L3, L5 Upper Limb: C5, C7	N=31 12 weeks 2 times/ week Sham-Electroacupuncture	BPI-SF FACT-TAX FACT-TNX NPS-4	No significant changes in the BPI-SF for the intervention group No significant changes in the FACT-NTX or FACT-TAX Significant difference between IG and CG at 16 weeks for NPS-4 and BPI-SF, the IG group reported worse pain
Kneis et al. (2019)	RCT	6/10	41 participants mean age 62 male and female Mixed cancer types Stage unknown Non-specified neurotoxic agents	N= 25 12 weeks 60 minutes Endurance training + Balance training Endurance training at moderate intensity for 30 minutes on a stationary bike Balance training for 30 minutes with three to eight exercises repeated three times for 20-30 seconds	N= 25 12 weeks 30 minutes Endurance training At a moderate intensity on a stationary bike	Vibration sense with tuning fork EORTC-QLQ-CIPN20 EORTC-QLQ-C30	The vibration sense did increase significantly in the CG at the patella ($p<0.002$) and the knuckle ($p<0.017$), it significantly decreased in the IG ($p<0.041$) QoL did not increase significantly in both groups In all subscales apart from the upper extremity, the IG group significantly decreased their CIPN

Lu et al. (2019)	RCT (pilot study)	5/10	40 participants mean age IG 54 CG 53 female Breast cancer Stage 1-3 Non-specified neurotoxic agent	N= 20 8 weeks Electroacupuncture Yin Tang Upper Limb: LI11, TW5, Baxie Lower Limb: SP-9, SP-36, SP-6, K-3, LR-3, Quidan	N= 20 8 weeks Usual care	Change in PNQ Change in FACT-NTX Change in BPI-SF Change in EORTC-QLQ30	The PNQ sensory score decreased significantly compared to CG ($p<0.011$), the motor score did not decrease significantly The FACT-NTX scores did decreased significantly in the IG compared CG ($p<0.002$) QoL did increase significantly in the IG group compared to the CG ($p<0.03$) The IG experienced a significant decrease in pain severity ($p<0.03$), average pain ($p<0.01$), and pain interference ($p<0.03$)
Molassiotis et al. (2019)	RCT	6/10	77 participants Mean age 57.1 Male and Female Mixed cancer types Stage 1-4 Non-specified neurotoxic agent	N=44 8 weeks 2 times/week 30-minute session Acupuncture If upper limbs affected: LI4, LI11, PC7, TE5 and/or Baxie If lower limb is affected: SP6, ST36, LV3, ST41 and/or Bafeng	N=43 8 weeks Usual care	BPI FACT-NTX TNSc	The pain intensity ($p<0.05$) and interference ($p<0.01$) measured by the BPI does decrease significantly after 8 weeks TNSc decreased significantly in the IG ($p<0.001$), but there were no significant between group differences The FACT-NTX showed significant improvements in the total score ($p<0.01$), the Ntx score ($p<0.01$), and the FACT-G score ($p<0.01$)
Ng et al.	RCT	5/10	38 participants Mean age IG 56.5 CG 53.6 Female Breast cancer Stage 1-3 Taxane neurotoxic agent	N=21 12 weeks Cryotherapy Hypothermia gloves or socks applied for a total of 90 minutes during chemotherapy infusion	N=17 12 weeks Control	PNQ EORTC-QLQ-C30 EORTC-QLQ-CIPN20	No significant difference between groups in the incidence of PNQ motor and sensory grades C-E, or the EORTC-QLQ-CIPN20 At 9 months post-paxitaxel the QoL showed significant increase

							compared to the CG (0.024) At 3 months post-paxitaxel the incidence of grade C-E PNQ motor scale was significantly less in the IG (p<0.012)
Rostock et al. (2013)	RCT	6/10	60 participants Mean age 49.9 Male and Female Mixed cancer types Stage unknown Taxane neurotoxic agent	N= 14 3 weeks 8 sessions Electroacupuncture Upper limb: LI4, LI11, SI3, HT3 Lower limb: LV3, SP9, GB41, GB43, treated depending on what is affected	3 weeks 8 sessions Vitamin B (N=13) Hydroelectric baths (N=15) Placebo (N=17) Three, highly dosed Vitamin B1/6 capsules taken each day Cross-galvanic baths were applied to the affected upper or lower limbs at 35°C for 15 minutes Placebo consisted of lactate capsule that should emulate the Vitamin B capsule	NRS Neuropathy score (sensory symptoms, sensibility, strength, vibration threshold, deep tendon reflexes) EORTC-QLQ30 (Global health)	No significant improvements were observed in any group No significant difference was observed between groups in the NRS
Streckmann et al. (2014)	RCT	6/10	56 participants Mean age IG 44 CG 48 Male and Female Mixed cancer types Stage 1-4 Non-specified neurotoxic agent	N= 28 36 weeks Twice a week Aerobic endurance training Sensorimotor training Strength training Aerobic endurance training was performed for 10-30 minutes on either a treadmill or a stationary bike During sensorimotor training four postural stability tasks were performed in three sets Strength training consisted of 4 resistance exercises performed for one minute	N= 28 36 weeks Standard clinical care including physiotherapy	EORTC QLQ-C30 Incidence of deep peripheral sensitivity disturbance	In the IG the incidence of deep peripheral sensitivity disturbances changed significantly compared to the CG (p<0.001) Significant within group change in the EORTC-QLQ-C30 QoL score (p<0.033), diarrhea (p<0.02), and constipation (p<0.05)

Zimmer et al. (2018)	RCT	6/10	30 participants Mean age IG 68.53 CG 70.00 Male and Female Colorectal cancer Stage unknown Mixed types of neurotoxic agents	N=17 8 weeks Two times/week 60 minutes Phase 1: 15 minutes balance and coordination training Phase 2: 30 minutes endurance training and resistance training Phase 3: 10-15 minutes cooldown	N=13 8 weeks Control	FACT-NTX	The Trial Outcome Index showed significant between group differences from baseline to 8 weeks ($p< 0.028$) and to the 4-week follow-up (0.031) with the score of the IG group remaining stable The FACT-G score did not show a significant difference between groups The Ntx subscale did show significant differences from baseline to 8 weeks ($p<0.002$) and 4-week follow-up ($p<0.015$)

Abbreviations: *BPI=Brief Pain Inventory, BPI-SFI=Brief Pain Inventory – Short Form, EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC-QLQ-CIPN20= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN 20 item scale, FACT-B=Functional Assessment of Cancer Therapy-Breast, FACT-NTX=Functional Assessment of Cancer Therapy-Neurotoxicity, FACT-TAX=Functional Assessment of Cancer Therapy-Taxane, NPS-4= neuropathic pain scale-4 item score, NRS=numeric rating scale, PNQ= Patient Neurotoxicity Questionnaire, TNS=Total Neuropathy Score, TNSc=Total Neuropathy Score clinical version*

Discussion

The aim of this systematic review was to compare the effectiveness of active interventions to passive non-pharmacologic interventions in the treatment of CIPN symptoms and decreased QoL in patients suffering from CIPN. The results of the Best Evidence Synthesis show that active interventions have stronger evidence for an overall positive effect on CIPN symptoms compared to the positive effect all passive interventions combined. They showed a positive effect on CIPN symptoms, however there's only limited evidence for it, while there is strong evidence for the positive effects of the active interventions on the reduction of CIPN symptoms. Looking at QoL both active and passive interventions showed limited evidence that they have a positive effect on this outcome. As a secondary outcome, the most common sources for a higher risk of biased were assessed, it showed that the criteria not met on the PEDro scale most often were regarding blinding of participants, therapists, and assessors as well as obtaining measures from 85% of participants for at least one key outcome.

There are several systematic reviews released concerning individual interventions, such as exercise therapy, acupuncture, electroacupuncture, and cryotherapy. Exercise therapy had a positive effect on CIPN symptoms and QoL, with a combination of endurance, resistance, and sensorimotor appearing to be most effective. (Duregon et al., 2018) Bailey et al. found that cryotherapy can decrease the incidence of CIPN, however they found conflicting evidence, which kept them from making a conclusion. (Bailey et al., 2021) It is also noteworthy, that they not only looked at RCTs, but also non-randomized and retrospective, cohort trials. Two systematic reviews investigated the effect of acupuncture and electroacupuncture, Chien et al. showed that acupuncture may decrease pain and increase QoL with Hwang et al. demonstrating that acupuncture is safe. Both reviews did not come to a conclusion as they both stated that there was too little high-quality evidence. These findings fit with what has been shown in this review, for individual passive intervention and all passive interventions combined there is limited evidence, while exercise interventions consisting of the same combination of interventions found to be most effective by Duregon et al. showed strong evidence for improving CIPN symptoms.

The exact mechanisms of CIPN are not fully understood yet and they seem to vary between the different neurotoxic agents used. (Zajaczkowską et al., 2019) Sensorimotor or balance training has been shown to have an effect on cortical excitability, with no effect on the spinal mechanisms. (Taube et al., 2007) A review by Taube et al suggested that there are additional neural adaptations happening on the spinal and corticospinal level, with all adaptations being task specific. (Taube et al., 2008) This indicates that balance training potentially leads to plastic changes in the central nervous system associated with better postural control. Additionally, a meta-analysis by Dinoff et al. found that aerobic training can increase the blood level of brain-derived neurotrophic factors (BDNF), while resistance training showed no such effect. BDNF appears to be an important factor for re-growth of peripheral neurons after injury via trkB and p75ntr pathways, with the latter displaying mixed findings. (McGregor & English, 2019) Whether or not these findings are applicable to CIPN mechanisms remains questionable.

The effect acupuncture has on the neurophysiology of the peripheral nervous system has been investigated by a systematic review by Bauemler et al., they found that acupuncture could decrease the pain pressure threshold and the sensation of noxious cold and hot stimuli. Another study suggested that bee venom acupuncture would alleviate oxiplatin-induced cold allodynia by activating the serotonergic inhibitory system.(Lee et al., 2014)Like-wise low-frequency EA has been shown to reduce cold allodynia after administrating one dose of oxiplatin in rats.(Moon et al., 2014) Next to

that, EA has shown to decrease cancer related pain (Zhang et al., 2014), however cancer pain involves a broader definition that neuropathic pain is a part of (Caraceni & Shkodra, 2019). The effect of cryotherapy on the peripheral nervous system in neurological disorders appears to not have been investigated, a study done on healthy athletes showed that cryotherapy may increase the pain threshold and tolerance with decreasing nerve conduction speed.(Algafly & George, 2007) If the different mechanisms in which active or passive interventions act upon the nervous system had an impact on the difference between the effects reported on the CIPN symptoms remains unclear.

One of the reasons why exercise therapy might have been shown to be more effective in the reduction of CIPN symptoms, could be the different methods of acquiring the outcome. Both types of interventions use the EORTC-QLQ-CIPN20 and FACT-NTX questionnaires, the first has been shown to be reliable and valid for health-related QoL and reporting CIPN symptoms. (Le-Rademacher et al., 2017; Smith et al., 2013) The same has been found for the FACT-NTX (D. F. Cella et al., 1993; Cheng et al., 2020), however the pinprick test and tuning fork test for deep peripheral sensitivity disturbance used only by active interventions have not been tested individually in a population suffering from CIPN. The tuning for test has been found to be reliable in diagnosing sensory and vibration perception in diabetic patients with deep peripheral neuropathy (Lanting et al., 2020), while the pinprick test has been shown to be valid detecting small-fiber degeneration in carpal-tunnel syndrome and diabetes.(Brown et al., 2017; Ridehalgh et al., 2018) Therefore, it remains unclear whether the usage of the pinprick test or the tuning fork test is reliable when testing for CIPN.

Next to that, a reason could be lying in the studies investigating acupuncture and EA being recruiting participants mainly in Western countries. Acupuncture has originated in Traditional Chinese Medicine (TCM) and focuses on the meridians and their collaterals that are running throughout the body transporting Qi. An imbalance between yin and yang is thought to be the cause of disease, that can be treated with needling specific acupoints taken from TCM.(Chen et al., 2019) When looking at western medicine, it is founded on a different concept, i.e. the National Cancer Institute defines western medicine as follows: “A system in which medical doctors and other healthcare professionals (such as nurses, pharmacists, and therapists) treat symptoms and diseases using drugs, radiation, or surgery. Also called allopathic medicine, biomedicine, conventional medicine, mainstream medicine, and orthodox medicine”. (NCI Dictionary of Cancer Terms - National Cancer Institute NCI Dictionary of Cancer Terms, 2013) This shows how medical treatment may be observed differently between the two cultures. As the passive treatments included in this review consisted mainly of acupuncture or electroacupuncture with recruiting patients in a western society, health belief could have had an impact on the results of these studies. As health belief has been identified as a factor that needs to be taken into attribution with treatment and therapy that can have an effect on their outcome (Vaughn et al., 2009). However in the past decades the acceptance of acupuncture has increased, as more studies have arisen that show acupuncture can be effective in the treatment of arthritis, migraines, and chronic pain (Jishun & Mittelman, 2014). So, whether or not the fact that acupuncture was applied in Western countries had an impact on the results of the studies remains questionable.

Another reason could lie in the usage of the BES as the method for data synthesis, as one moderate quality article could already exclude the option of having strong evidence. In this review the only two moderate quality studies were investigating passive interventions, as there were six studies in total, the two moderate quality studies made up 1/3rd of all the articles. It appears that the passive interventions currently do not have enough high-quality studies conducted, with the active interventions having higher quality studies done. However, it is not predetermined that active interventions show better outcomes, even if passive non-pharmacologic interventions can only display moderate evidence, the BES is still founded on the individual outcomes of the studies. Meaning that if the active interventions would have found no significant improvements, the passive

interventions would have still had better evidence for them. There might still be an indication that more high-quality studies investigating passive non-pharmacologic interventions are needed.

Strong & weak points

A limitation of this study was the inclusion of few articles, especially for individual passive interventions, as this makes the results of this review less reliable and had a negative impact on the conclusion. However, this was due to wanting to assess both CIPN symptoms and QoL, the latter was added as an outcome as there are indications in previous research that QoL is an outcome that is negatively affected in cancer patients. (Nayak et al., 2017) To be able to investigate the effect of an intervention on both, the RCTs had to include measurements related to both outcomes. Next to that, this review was not focused on individual interventions, but on active and passive interventions combined.

Another limitation is the usage of the BES, as it does not account for different population sizes per study, which did vary widely across the studies included. Nonetheless, using the BES allowed for a comparison of the included studies, even if data was missing for conducting an effect size analysis and there was no heterogeneity in the measurement instruments. Additionally, the number of participants was an influential factor for the quality assessment of the studies, so it has been accounted for in the analysis.

Furthermore, the search strategy varied for the different platforms, meaning that the method of retrieving articles was not consistent, reducing the methodological quality of the review. Nonetheless the combination of the same search terms has led to no results on one of the platforms or too many search results, therefore adjustments had to be made to the original search strategy leading to different search strings per platform..

Lastly, the generalizability of the results is limited as the population included in this review consisted mainly of women diagnosed with breast cancer, making the results of this study less applicable to the general population diagnosed with cancer. However, the most common type of cancer diagnosed is breast cancer mainly affecting women (World Health Organization, 2020). Meaning that the results would still apply to a large portion of the general population, next to that half of the studies included did also include participants with other types of cancer.

A strength of this review lies in the good quality of the included articles, as eight out of the ten included articles are rated “good” quality RCTs based on the PEDro scale. Next to that there was a large group of participants included in this review, both points make the results of this review more reliable. Furthermore, this review looked into QoL next to the CIPN symptoms, as QoL was rated below average by 82.3% of patients having undergone treatment for their cancer in a study conducted by Nayak et al. Additionally, Shrestha et al found that cancer patients seem to value their QoL of live just as much as the length of their life (LoL) in their review, with some of the included studies reporting patients valuing QoL more than LoL under certain circumstances (Shrestha et al., 2019). Which makes it important to assess it as an outcome next to CIPN symptoms.

Conclusion

There is an indication that active interventions are more effective than passive interventions in the treatment of CIPN symptoms in patients undergoing or having undergone chemotherapy. It remains unclear whether active or passive interventions are more effective in treating decreased QoL, as evidence was limited. However, further research needs to be conducted to have more high-quality studies for a better comparison that allows for stronger evidence behind recommendations made. Especially, QoL-related outcomes should be included more into research, additionally there is a need for more RCTs on the different passive interventions.

Relevance

As this is the first literature review that is comparing two types of interventions and their effect on CIPN symptoms, it can give a first direction for practitioners what treatment they could choose when encountering patients diagnosed with CIPN. The results of this review can be applied in rehabilitation centers or in private practices that encounter patients diagnosed with CIPN and experiencing CIPN symptoms. There are implications that for the treatment CIPN symptoms exercise therapy should be chosen over passive non-pharmacologic interventions such as acupuncture, electroacupuncture, or cryotherapy. For improving QoL no recommendations can be made based on the included studies, further research needs to be conducted in order to be able to give practice recommendations. A general consideration for further studies should be to include a measurement tool related to QoL, as it has shown to be affected in many cancer patients undergoing treatment (Nayak et al., 2017) and for this review many studies had to be excluded due to lacking an outcome related to QoL. Next to that, consensus on the usage of measurement instruments needs to be established as there is no Golden Standard developed for patient-reported CIPN symptoms (Smith et al., 2018) or quantitative sensory testing (Martland et al., 2020) yet.

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Appendices

Appendix 1 – Search string per platform

PubMed

Search string	Filter	Results
"CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation"		N=27.850
"CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation"	10 years, full text, randomized controlled trial	N= 16.131
CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation" AND “quality of life”	10 years, full text, randomized controlled trial	N= 3.431
CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation" AND “cancer”	10 years, full text, randomized controlled trial	N= 1.018
CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation" AND “cancer” AND “Quality of Life”	10 years, full text, randomized controlled trial	N= 494
CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" AND “quality of life” AND “cancer”	**10 years, full text, randomized controlled trial**	**N= 63**

SpringerLink

Search string	Filter	Results
"CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation"	Article, English	N= 161.456
CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation" AND “quality of life”	Article, English	N= 70.567
CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation" AND “cancer”	Article, English	N= 34.678

CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation" AND “cancer” AND “Quality of Life”	Article, English	N= 0
CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" AND “quality of life”	**Article, English**	**N= 326**

CINHAL

Search string	Filter	Results
"CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment" OR "rehabilitation"		N= 1
CIPN" OR "chemotherapy-induced peripheral neuropathy" AND "treatment"	**Full text, 2011-2021, English**	**N=115**

Appendix 2 – PEDro scale per study

Criteria/Study	Bland et al. (2019)	Greenlee et al (2016)	Kneis et al. (2019)	Lu et al. (2019)	Molassiotis (2019)	Ng et al. (2020)	Rostock et al. (2013)	Streckmann et al. (2014)	Zimmer et al. (2017)
Eligibility criteria were specified	YES (p. 2)	YES (p. 2-3)	YES (p. 2)	YES (p. 2)	YES (p. 2)	YES (p. 2)	YES (p. 2)	YES (p. 2)	YES (p. 3)
Subjects were randomly allocated to groups	YES (p. 2)	YES (p. 3)	YES (p. 2)	YES (p. 2)	YES (pp. 2-3)	YES (p. 2)	YES (p. 2)	YES (p. 2)	YES (p. 3)
Allocation was concealed	YES (p. 2)	NO	YES (p. 2)	NO	NO	NO	YES (p. 2)	NO	NO
The groups were similar at baseline regarding the most important prognostic indicators	YES (p. 7)	YES (p. 5)	YES (p. 6)	YES (p. 4)	YES (p. 7)	YES (p. 5)	YES (pp. 4-5)	YES (p. 5)	YES (p. 5)
There was blinding of all subjects	NO	YES (p. 3)	NO	NO	NO	NO	NO	NO	NO
There was blinding of all therapists administering therapy	NO	NO	NO	NO	NO	NO	NO	NO	NO
There was blinding of assessors who measured at least one key outcome	NO	NO	NO	NO	NO	NO	NO	NO	YES (p. 3)
Measures from at least one key outcome were obtained from more than 85% of the subjects	NO	NO	NO	NO	YES (p. 6)	NO	NO	YES (p. 4)	NO
All subjects for whom outcome measures were available received the treatment or control condition as allocated	YES (p. 5)	YES (p. 4)	YES (p. 6)	YES (p. 7)	YES (p. 3)	YES (p. 6)	YES (p. 3)	YES (p. 3)	YES (p. 3)
The results of between-group statistical comparisons are reported for at least one key outcome	YES (p. 4)	YES (p. 19)	YES (p. 6)	YES (p. 6)	YES (p. 7)	YES (pp. 6-8)	YES (p. 6)	YES (p. 4)	YES (p. 6)
Score	6/10	6/10	6/10	5/10	6/10	5/10	6/10	6/10	6/10