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SYSTEMATIC REVIEW

Conservative non-pharmacological treatments for chemotherapy-induced peripheral neuropathies in women treated for breast cancer: a systematic review

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ABSTRACT

INTRODUCTION: Over the last few decades, the use of neo/adjuvant therapies has significantly increased the number of breast cancer survivors who experience chemotherapy-induced peripheral neuropathy (CIPN). To date, few, low-efficacy, pharmacological remedies exist to manage this side effect. For this reason, alternative treatments are increasingly being investigated as possible strategies to prevent or promote faster recovery from CIPN. In this review we aimed to provide an overview of the literature evidence regarding all the non-pharmacological and rehabilitative interventions for patients affected by CIPN secondary to breast cancer care.

EVIDENCE ACQUISITION: A comprehensive literature search was conducted on PubMed, Scopus and Web of Science and included a total of 1895 patients (1528 with breast cancer) with a wide range of CIPN (motor, sensory and autonomic neuropathies) and chemotherapy treatments (*e.g.*, Taxanes, Platins, Vinca alkaloids or monoclonal antibody drugs).

EVIDENCE SYNTHESIS: Of the initial 1108 hits, only 25 studies – describing different treatment modalities for peripheral neuropathies – were finally included in the qualitative synthesis. Most studies focused on acupuncture, physiotherapy, cryotherapy, and yoga.

CONCLUSIONS: There is still controversial evidence on conservative non-pharmacological interventions for the management of CIPN symptoms. We believe however that moderate exercise, as well as all types of stress reducing activities like sport, yoga and mindfulness, should be encouraged in cancer patients for their positive effect on global physical and psychological health. Further studies of higher methodological quality are needed to determine the best conservative approach to CIPN.

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KEY WORDS: Physical therapy modalities; Yoga; Cryotherapy; Acupuncture.

Introduction

In the last few decades, the use of neo/adjuvant therapies has significantly increased the number of breast cancer survivors who experience long-term side effects due to antineoplastic agents.[1, 2] Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most frequent consequences of many commonly used chemotherapeutic

drugs with significant impact on quality of life. CIPN has a prevalence of 68.1% in the first month after chemotherapy, and of 30% at 6 months;[3] 58.4% of patients report persistent CIPN symptoms even after an average follow-up time of 5.6 years.[4] Neural toxicity can arise after single treatments or due to cumulative exposure to neurotoxic drugs and may be enhanced by predisposing factors like diabetes mellitus, older age, concomitant exposure to other neurotoxic agents, pre-existing neuropathy, and deficiency diseases.[5, 6] Chemotherapy tends to damage cellular bodies in the dorsal root ganglion where they are less protected by the blood-brain barrier. This explains the predominance of sensory neuropathy with symmetrical distribution and length-dependency (dying assonopathy).[6]

The clinical presentation of CIPN much depends on the specific antineoplastic drug used, the dose and the timing of administration.[7, 8] In most cases it manifests just after a few doses and it is characterized by a predominant sensory involvement (*e.g*., "glove and stoking" paresthesia, tingling, numbness, and neuropathic pain) leading to impairment with walking, balance, and fine motor tasks.[9] More rarely, it can manifest with motor and autonomic disturbances.[7] Taxanes are the most used class of drugs in the treatment of breast cancer.[10] This class is associated with arthralgias, myalgias, paresthesia, ataxia, proximal weakness and loss of thermal sensitivity and proprioception. Similar symptoms may be experienced with platin-based antineoplastic drugs.[11] Vincristine is associated with mixed sensory, autonomic and motor neuropathy and cranial nerve palsy.[11] Finally, most antineoplastic agents are associated with a delayed worsening of symptoms in the months following the completion of treatment ("coasting phenomenon").[11]

Unfortunately, there is an unmet need for therapies for CIPN. To date, very few drugs were found to be useful in prevention or treatment of this side effects. Moreover, there is lack of consensus about the standard way to identify affected patients, as well as those who are at higher risk for developing severe symptoms.[9] For the management of CIPN, only Duloxetine finds a moderate recommendation for painful CIPN,[5] while tricyclic antidepressants and anticonvulsants have shown either inefficacy or limitation due to side effects.[12] Pregabalin and gabapentin are largely used drugs for the management of neuropathic pain of different nature, however several double-blind placebo-controlled trials failed to show any benefit against CIPN symptoms.[13, 14]

Acetyl-L-carnitine, which is another commonly prescribed drug for neuropathic disorders, is not recommended as a therapy to prevent or treat CIPN. Indeed, in some studies it was associated with more severe CIPN symptoms.[15] For this reason, non-pharmacological and rehabilitative interventions are increasingly being investigated as alternative approaches to alleviate or promote faster recovery from CIPN. At present, several studies have been conducted to assess the effect of different interventions (*e.g*., acupuncture, physiotherapy, cryotherapy, and herbal remedies) on CIPN, however the literature still does not provide a standard recommendation for their use.[16] Given the high prevalence of patients with breast cancer who undergo chemotherapy, we aimed to provide a systematic review of the literature regarding all the non-pharmacological and rehabilitative interventions for patients affected by CIPN secondary to breast cancer care.

Evidence acquisition

Search strategy

A comprehensive literature search was conducted on PubMed, Scopus and Web of Science using the following terms in different combination: "chemotherapy," "peripheral neuropathy," and "breast cancer." All studies focusing on conservative non-pharmacological treatment or rehabilitation of chemotherapy induced peripheral neuropathies in women treated for breast cancer were assessed for eligibility. Only randomized controlled trials (RCTs) or quasi-RCTs published in the last decade up to May 19th, 2023, and written in English language were included.

Study selection

Based on the PICO guidelines, selection criteria for the studies were limited to adult patients of both sexes affected by any type of CIPN following chemotherapy treatment for breast cancer. Outcomes related to general function, strength, quality of life, and pain were extracted. All papers taking in consideration pediatric patients or patients with previous neuropathies or non-CT related neuropathies were excluded. Eligibility criteria are summarized in Table I.

Data extraction

To reduce the risk of inter-observer bias, two independent authors selected the eligible articles for the review. In case of disagreement in the article selection or data extraction process, a third person was involved. Data extracted from the selected studies were patients' characteristics (number, mean age, baseline pathology), type of chemotherapy, type of neuropathy (motor or sensory, axonal or demyelinating, small or large fiber), type rehabilitative intervention (ex-

TABLE I.—*Study eligibility criteria (PICO).*

Criteria	Inclusion	Exclusion
Population	Adult of both sexes treated with chemotherapy for breast cancer and affected by CIPN	Pediatric population, non-CT related neuropathies
Intervention	Any non-pharmacological or rehabilitation intervention for CIPN	
Comparison	Any non-pharmacological treatment or placebo for CIPN	
Outcome	sensitivity, function, strength, pain, quality of life	
Date	Last 10 years	
Language	English	

perimental and control intervention), outcome measures, rehabilitation timing, and main results (Supplementary Digital Material 1: Supplementary Table I).[15, 17-39]

Methodological quality

The methodology of this study was reported following the PRISMA statement for systematic review and meta-analysis.[40] The Cochrane library assessment tool and the PEDro scale were respectively used to evaluate the risk of bias and the methodological quality in all the 25 selected studies respectively.[41, 42] The Cochrane tool includes seven domains (*i.e.*, sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other sources of bias). A green light is assigned to a low risk of bias, a yellow light to an unclear risk of bias and a red light to a high risk of bias (Figure 1).[15, 17-39, 43] The PEDro scale is based on the Delphy scale for quality assessment of RCTs and includes 11 domains. A positive (green dot) or negative (red dot) score is assigned to each domain based on whether a criterion is met or not. According to the final score, the study quality is classified as follow: "high" (score ≥6), "fair" (between 4-5) and "poor" (score ≤3) (Figure 2).[15-20-43]

Evidence synthesis

A comprehensive search was conducted on PubMed, Web of Science and Scopus search engines and identified 1108 hits. After removal of duplicates, 707 articles were reviewed by title and abstract, 72 full-text articles were assessed for eligibility, and 25 studies were finally included in qualitative synthesis (Figure 3).

A total of 1895 participants (1528 patient with breast cancer) were included in this systematic review with a wide range of CINP (motor, sensory and autonomic) and chemotherapy treatments (*e.g.*, Taxanes, Platins, Vinca alkaloids or monoclonal antibody drugs). Patients were mostly women with a mean age of 54 years. The numbers were calculated on 19 out of 25 papers, as six of them[17-23]

Figure 1.—Evaluation of the risk of bias. [15-20-43]

Figure 2.—Methodological quality assessment of the included studies with the PEDro scale. [15-20-43]

did not provide enough details in the text. The main results of each selected paper are summarized in Supplementary Table I.

Methodological quality synthesis

The Cochrane library assessment tool was used to evaluate the risk of bias for all the RCT studies included.[41] The

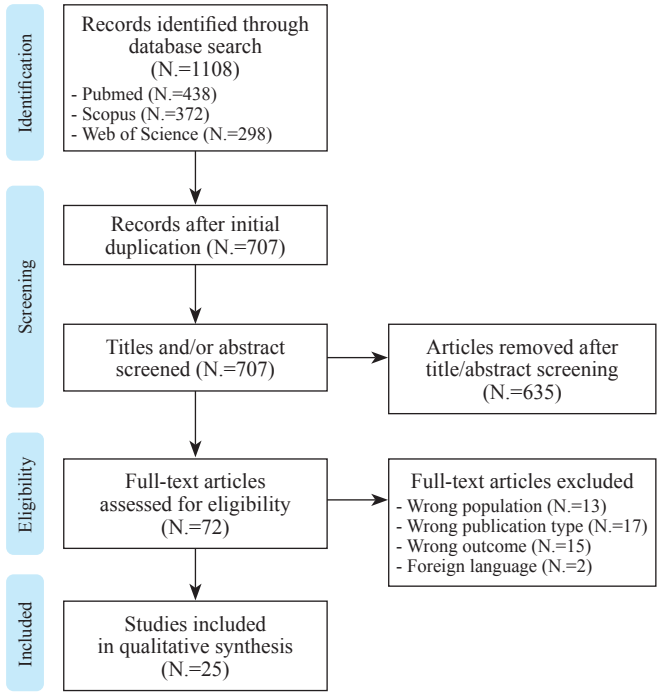

Figure 3.—Study selection process.

overall methodological quality of the cited studies was low. Except for two trials,[24, 25] almost all the studies presented multiple bias in terms of blinding of participants and personnel and blinding of the outcome data (Figure 1). In terms of methodological quality all the included studies reached a score of at least 6/10 on the PEDro scale which classifies them as "high quality" (Figure 2).

Study design

Treatment modalities for CIPN were very heterogeneous: six studies investigated the effect of acupuncture,[15, 23, 26-29] four studies investigated conventional physiotherapy *versus* standard care,[17, 30, 31, 43] five studies, the application of cryotherapy,[20, 21, 32-34] one study compared physical exercise *versus* cold application,[22] three studies investigated the effect of yoga,[18, 35, 36] and six studies, the application of other miscellaneous interventions such as electroencephalogram (EEG) with neurofeedback (NFB),[37] hand and feet massage,[19] mindfulness-based stress reduction,[38] electrostimulation,[25] neurolaser[24] and gloves compression therapy.[39]

Outcome measures

Significant heterogeneity was encountered in terms of outcome measures and rating scales. For quality-of-life

assessment, eight studies used the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale (EORTC-QLQ-CIPN20),[18, 19, 21, 23, 25, 31, 32, 34] two studies used the Short Form-36 (SF-36) questionnaire,[37, 38] and one study used the World Health Organization Quality of Life scale Brief Version (WHOQOL-BREF).[29] Patients' neurotoxicity was mostly assessed with subjective questionnaires: three studies used the Patient Neurotoxicity Questionnaire (PNQ),[20, 21, 26] three studies, the Total Neuropathy Score (TNS),[24, 25, 43] two studies used quantitative sensory testing (*e.g.*, vibration, pinprick, pressure),[17, 31] and only two studies included an objective neurophysiological evaluation, using nerve conduction studies (NCS).[19, 21] For functional assessment, six studies used the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - neurotoxicity (FACT-GOG-NTX),[20, 23, 26, 28, 29, 33] three studies, the Functional Assessment of Cancer Therapy-Taxane (FACT-Tax),[15, 24, 33] one study, the Functional Assessment of Cancer Therapy - General (FACT-G),[23] one study the Functional Assessment of Cancer Therapy - Breast (FACT-B),[25] while other studies included the DASH scale,[17] functional reach tests,[36] and the 6-minute Walking Test (6MWT).[24] For pain evaluation, the most used scales were the Brief Pain Inventory-short form (BPI-SF)[15, 26, 29, 37] and the numerical rating scale (NRS) for pain.[17, 18, 25, 27, 36]

Discussion

CIPN is an adverse event of many commonly prescribed chemotherapeutic agents. Current symptomatic therapies are few and have demonstrated limited efficacy. In this review we aimed to provide a summary of the evidence regarding non-pharmacological and rehabilitative interventions available for CIPN secondary to breast cancer care. We included 25 RCTs describing different treatment modalities for CIPN. Most studies, however, focused on four main treatments such as acupuncture,[15, 23, 26-29] physical therapy,[17, 22, 30, 31, 37, 43] cryotherapy,[20, 21, 32-34] and yoga.[18, 35, 36]

Acupuncture

Acupuncture is an ancient Chinese remedy for the treatment of acute and chronic pain. It consists of the insertion of fine needles (manipulated by hand or by electrical stimulation) into specific anatomical locations to stimulate the peripheral and central nervous system.[26, 44] Previously published evidence on the efficacy of this procedure, has led to a multiplication of approaches including the treatment of chemotherapy-related side effects.[44] In this review, we reported 6 trials that focused on this treatment. In a randomized cross-over pilot trial Lu *et al.*[26] compared 8 weeks of manual acupuncture *versus* usual care. At the end of the experiment, acupuncture led to a statistically and clinically significant improvement in sensory (PNQ), functional (FACT-GOG-NTX) and pain (BPI-SF) severity scores compared with the control arm. Furthermore, no serious side effects were observed. Likewise, another trial by Bao *et al.*[36] compared 8 weeks of electroacupuncture against sham acupuncture or usual care, and found the greatest reduction of pain, tingling, and numbness in the treatment group. Reported adverse events were also few and mild in this case. Finally, the study of Kim *et al.*[23] investigated the effects of self-acupressure *versus* no treatment on daily life activities and quality of life and found a significant improvement in all the outcomes scores in the treatment group compared with the control group. On the other hand, 3 trials found only partial or non-significant advantage of applying acupuncture *versus* sham therapy. Specifically, Bao *et al.*[28] found a non-statistically significant difference between the experimental and the control group on quality-of-life outcomes. However, important differences in terms of baseline tumors, chemotherapy regimens and years since chemotherapy (5.4 *vs.* 3.0 years) between treatment and control groups were reported. Greenlee *et al.*[15] found no difference in terms of pain, function and other CIPN symptoms. Huang *et al.*[29] found a greater improvement in the acupuncture group only in touch perception and pain severity, while non-significant differences were found in terms of functional and quality of life scores. Findings should be considered with caution since these studies included a small sample size and, in one case,[28] a significant difference in the interval between chemotherapy completion and acupuncture beginning (277.90 *versus* 115.90 days) existed between the tested groups. Furthermore, in Bao *et al.*[28] the sham acupuncture procedure consisted of "minimal needling" instead of the commonly used "no puncture approach". Regarding the adverse events, only one case of acupuncture needle site reaction with discomfort, minor swelling, and bruising was reported by Greenlee *et al.*[15] Considering the small sample size of the cited studies and the presence of several methodological bias, these results are in line with the literature which reports controversial evidence of effectiveness of acupuncture for the management of CIPN symptoms.[44, 45]

Physiotherapy

Exercise during chemotherapy has yielded promising results as an option to prevent and slow down CIPN de-

velopment.[46, 47] Andersen-Hammond *et al.*[17] investigated the effect of a home-based daily exercise program *versus* standard care. The program, consisted of nerve gliding, stretching, axillary webbing exercises and range of motion (ROM) exercises for the neck and upper limb, performed at the beginning of the Taxane-chemotherapy. Overall, the experimental group showed less pain and improvement in pressure thresholds and grip dynamometry compared to the control group. Furthermore, subgroup analysis, showed a higher preservation of vibration, heat and pain thresholds in the more active participants compared with the more sedentary ones. The study of Kleckner *et al.*[30] suggests that six weeks of exercise during chemotherapy reduced the prevalence and severity of CIPN symptoms, as assessed by patient reports of numbness and tingling and hot/coldness sensation in the hands and feet. Conversely, the study of Muller *et al.*[43] – which investigated the preventive effect of sensorimotor exercise training or resistance training *versus* usual care – found that none of the exercise programs were able to significatively impact on the progression of CIPN. In the exercise adherent group, however, an overall improvement was observed in subjective perception of sensory symptoms in the feet, muscular strength, quality of life, physical and role functioning, fatigue and pain *versus* usual care. Furthermore, compliance to chemotherapy was found to be enhanced in this group. A similar result was obtained by Bland *et al.*[31] which randomized 27 patients with breast cancer, during Taxane-chemotherapy, to immediate exercise *versus* delayed exercise. The protocol included supervised aerobic, resistance, and balance training 3 days a week for 8-12 weeks. At the end of the chemotherapy, no difference was found between groups for numbness and vibration sense in the toes. Similar to Muller *et al.*,[43] the immediate exercise group, however, showed a higher global health status and quality of life compared to the control group, yet both groups had worse EORTC QLQ-CIPN20 sensory and motor symptom scores relative to baseline. Finally, Simsek *et al.*[22] compared a standardized 12-week home-based exercise program involving progressive strengthening, stretching, and balance exercises *versus* cold application and standard care. They found that exercise reduced CIPN symptoms of numbness in the hands and feet significantly more than cold application and controls.

Based on these results, the proves about exercise efficacy in the prevention or in the progression of CIPN in breast cancer patients are, to a certain extent, promising but still insufficient. This observation is in line with previous literature studies.[48] There is a general consensus that exercise should be encouraged in cancer patients for its effect on global health. Aerobic exercise is of benefit for the cardiovascular system, reducing fatigue and improving the endurance; anaerobic training stimulates muscle contraction and maintenance of muscle mass; proprioceptive exercise improves postural control reducing the risk of falls which is another bothersome consequence of sensory impairment.[46, 47] In addition, exercise during chemotherapy appears to result in an increased tolerance to treatment and fewer reductions or cancellations of the drug dose (Bland).[31] Higher-quality studies are needed to provide more definitive results on the effects of specific exercise types, frequency, intensity, and time from chemotherapy on specific types of CIPN.

Cryotherapy

Cold application has been suggested as a mean to slow down the occurrence of CIPN. The mechanisms through which it exerts its effect are several and include: 1) local vasoconstriction, which decreases the blood flow and the cellular metabolism; 2) reduction of nociceptors sensitivity, by decreasing the release of vasodilator substances; and 3) reduction of nerve conduction speed and muscle excitability.[22] A randomized trial of Shigematsu *et al.*[20] compared the application of cold mittens and slippers *versus* standard care. Compared to the control group, the experimental arm showed a marked decrease in sensory and motor neuropathy symptoms, and a marked improvement in functional scores. Moreover, no serious side effects were reported associated with cryotherapy. Similar results in terms of peripheral neuropathy severity and frequency were obtained in other two studies by Jue *et al.*[33] and Ruddy *et al.*[34] In the study of Jue *et al.*[33] however, no significant difference was found between experimental and control groups in terms of quality of life. Conversely, a trial of Beijers *et al.*[32] found a non-significant improvement in neuropathy symptoms in the hands of the experimental group wearing frozen gloves during chemotherapy. Yet, in this case, the authors reported that one-third of the frozen gloves group discontinued the study before the end of the treatment. Another randomized trial of Ng *et al.*[21] found no significant difference in CIPN symptoms severity between cryotherapy and usual care 2 weeks after Paclitaxel treatment, nonetheless a benefit was observed at 3 months both in the PNQ and EORTC QLQ-CIPN20 scores and in some neurophysiology parameters. However, the positive effect was not sustained in the long term. A limitation of this study is that temporary interruption of cryotherapy occurred in 80.9% of the subjects due to cold intolerance which could have affected the results. Overall, cryotherapy showed a good safety profile and

some promising results, however strong doubts remain about its tolerability as an alternative treatment for CIPN. Literature data on its efficacy are mixed.[20, 49]

Yoga

Yoga is a mind-body intervention that incorporates physical postures, breathing, and meditation to increase body flexibility and strength, body awareness, balance and relaxation.[18, 35] Knoerl *et al.*[18] compared 8 weeks of yoga against usual care and found that yoga, either in-person or in virtual sessions, led to statistically and/or clinically significant improvement in several cancer treatment-related symptoms (*i.e.*, depression, fatigue, sleep-impairment, anxiety). Yoga participants experienced significant within-group improvements in all the outcomes including CIPN symptoms, but only fatigue and depression were significantly improved compared with the control group. Moreover, no differences were found between in-person and virtual yoga group participants. Adverse events were few mild and included foot pain, Achilles tendonitis, and back pain. Similarly, Bao *et al.*[36] found that 8 weeks of yoga induced a statistically significant improvement in mean pain scores (NRS), function (FACT-GOG-Ntx) and risk of falls (functional reach test) compared to usual care. Conversely, no statistically significant change was observed in neuropathy symptoms for yoga *versus* usual care. Adverse events related to yoga were few and mild and included three cases of myalgia and one case of leg cramps. Finally, a study of Zhi *et al.*[35] found that 8 weeks of yoga were effective at reducing anxiety scores compared to the control group. However, no significant differences were found in depression, fatigue, or insomnia between yoga and waiting-list controls. Yoga seems a safe and good remedy for depression, fatigue, and sleep impairment in patients with breast cancer, however there is no direct evidence of efficacy for CIPN symptoms. Previous studies have shown that loss of somatosensory information caused by neuropathy significantly affects postural strategies, leading muscle co-contractions and related postural instability.[50] In this sense, yoga could be a valid aid to improve balance and physical posture and indirectly contrast the effect of CIPN. Moreover, virtual sessions could increase accessibility of rural residents, who may face difficulties to access oncology rehabilitation services.

Other treatments

The study of Song *et al.*[25] found no differences between patients treated with low-frequency electrostimulation (ES) immediately after chemotherapy *versus* sham therapy. Prinsloo *et al.*[37] found that electroencephalogram (EEG) neurofeedback showed greater improvement in cancer-related symptom severity (*e.g.*, pain and numbness), symptom interference, physical functioning, general health, and fatigue compared with waiting list controls. Furthermore, EEG showed neurological changes in the cortical location and in the bandwidth targeted by the intervention, and changes in EEG activity were predictive of symptoms reduction. In the study of Izgu *et al.*[19] 12 weeks of hands and feet classical massage showed higher improvement in neuropathic pain and quality of life scores over usual care. Furthermore, nerve conduction studies (NCS) showed a higher sensory action potential amplitude in the median nerve and a shorter tibial nerve latency in the massage group compared to the control group at week 12. Joy *et al.*[24] investigated the effect of photobiomodulation (PBM) during Taxane treatment and found a significantly higher FACT-GOG-Taxane and a borderline significant difference in the 6MWT and pain level compared to the control group. Kotani *et al.*[39] investigated the effect of compression therapy with surgical gloves *versus* no treatment in patients undergoing paclitaxel chemotherapy and found a non-statistically significant effect on the incidence of paclitaxel-induced peripheral neuropathies. Shergill *et al.*[38] randomized 98 breast cancer survivors with CIPN to an 8-week group mindfulness-based stress reduction (MBSR) intervention or a waitlist control group and did not find significant benefits of MBSR for the management of CIPN. Based on these results there is not enough evidence to draw any conclusion about the application of low-frequency electrostimulation, surgical gloves compression therapy and MBSR for CIPN. The effect of EEG neurofeedback, classical hand/feet massage and photobiomodulation might be further investigated in the near future.

Limitations of the study

This review has some limitations that must be noted. First, most of the studies presented a low methodological quality. Second, in most cases the heterogeneity of protocols and outcome measures used did not allow for a proper comparison of treatments between studies. Furthermore, it is not often clear what the authors mean with "standard or usual care" when comparing a treatment. Third, the temporal limitation to the last 10 years might have excluded other good quality RCTs. Fourth, some studies had a small sample size.

Conclusions

There is still controversial evidence of effectiveness of conservative non-pharmacological and rehabilitation

treatments for the management of CIPN symptoms. Cryotherapy showed some promising results, but strong doubts remain about its tolerability as an alternative treatment for CIPN. We believe that moderate exercise and all types of stress-reducing activities like yoga, mindfulness or meditation should be encouraged in patients with cancer for their positive effect on global physical and psychological health. At present, there is not enough evidence to draw any conclusion about the application of low-frequency electrostimulation, surgical gloves compression and MBSR for CIPN symptoms. Likewise, the positive effects observed with EEG neurofeedback, classical hand/feet massage and photobiomodulation need to be further investigated in larger studies. In conclusion, studies of higher methodological quality are strongly encouraged to determine the best rehabilitation approach to CIPN.

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