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Rehabilitation, exercise, and related non-pharmacological interventions for chemotherapy-induced peripheral neurotoxicity: Systematic review and evidence-based recommendations

Stefano Tamburin[a,*], **Susanna B. Park**[b], **Angelo Schenone**[c,d], **Elisa Mantovani**[a], **Mehrnaz Hamedani**[c], **Paola Alberti**[e], **Vesile Yildiz-Kabak**[f], **Ian R. Kleckner**[g], **Noah Kolb**[h], **Miryam Mazzucchelli**[i], **Brendan L. McNeish**[h], **Andreas A. Argyriou**[j], **Guido Cavaletti**[e], **Ahmet Hoke**[k], **Toxic Neuropathy Consortium**[1]

[a]Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Italy

[b]Brain and Mind Centre, Faculty of Medicine and Health, University of Sydney, New South Wales, Australia

[*]Corresponding author at: Section of Neurology, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Piazzale Scuro 10, I- 37134 Verona, Italy. stefano.tamburin@univr.it (S. Tamburin).

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Author contributions

Stefano Tamburin: conceptualization, data curation, formal analysis, methodology, project administration, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work.

Susanna B. Park: conceptualization, methodology, project administration, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Angelo Schenone: conceptualization, methodology, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Elisa Mantovani: conceptualization, data curation, formal analysis, methodology, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Mehrnaz Hamedani: conceptualization, data curation, formal analysis, methodology, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Paola Alberti: validation, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Vesile Yildiz-Kabak: validation, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Ian R. Kleckner: validation, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Noah Kolb: validation, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Miryam Mazzucchelli: validation, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Brendan McNeish: validation, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Andreas A. Argyriou: validation, supervision, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Guido Cavaletti: validation, supervision, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Ahmet Hoke: validation, supervision, data analysis and interpretation, writing (original draft, review & editing), final approval of manuscript, accountable for all aspects of the work

Toxic Neuropathy Consortium: conceptualization, project administration, accountable for all aspects of the work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2021.103575.

[c]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal and Infantile Sciences (DINOGMI), University of Genoa, Italy

[d]IRCCS San Martino Hospital, Genoa, Italy

[e]Experimental Neurology Unit, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

[f]Faculty of Physical Therapy and Rehabilitation, Hacettepe University, Ankara, Turkey

[g]Department of Pain and Translational Symptom Science, University of Maryland School of Nursing, Baltimore, MD, USA

[h]Department of Neurological Sciences, University of Vermont, Burlington, VT, USA

[i]School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

[j]Department of Neurology, “Saint Andrew’s” State General Hospital of Patras, Patras, Greece

[k]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Pharmacological strategies for chemotherapy-induced peripheral neurotoxicity (CIPN) are very limited.

We systematically reviewed data on rehabilitation, exercise, physical therapy, and other physical non- pharmacological interventions and offered evidence-based recommendations for the prevention and treatment of CIPN.

A literature search using PubMed, Web of Science and CINAHL was conducted from database inception until May 31st, 2021.

2791 records were title-abstract screened, 71 papers were full-text screened, 41 studies were included, 21 on prevention and 20 on treatment of CIPN. Treatment type, cancer type, chemotherapy compounds were heterogeneous, sample size was small (median: N = 34) and intention-to-treat analysis was lacking in 26/41 reports.

Because of the methodological issues of included studies, the reviewed evidence should be considered as preliminary. Exercise, endurance, strength, balance, and sensorimotor training have been studied in low-to- moderate quality studies, while the evidence for other treatments is preliminary/inconclusive. We offer recommendation for the design of future trials on CIPN.

Keywords

Chemotherapy-induced peripheral; neurotoxicity (CIPN); Evidence-based medicine; Exercise; Physical therapy; Rehabilitation; Treatment

1. Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a predominantly sensory neuropathy that may be accompanied by motor and autonomic changes (Cavaletti et al., 2019). CIPN symptoms are numbness, tingling, burning, shooting pain, impaired sensation,

cramps, and loss of strength, proprioception, and deep tendon reflexes, often distributed in a stocking-and-glove pattern (Wolf et al., 2008).

Chemotherapeutic agents that may induce CIPN include cornerstone anticancer drugs, such as platinum compounds, taxanes, vinca alkaloids, proteasome inhibitors, and other compounds (Cavaletti et al., 2019; Wolf et al., 2008; Loprinzi et al., 2020a; Staff et al., 2019; Tamburin et al., 2019). CIPN can be a disabling complication following the treatment of many types of cancer, including breast, colorectal and gastrointestinal, testicular, and hematological malignancies (Park et al., 2013).

The estimated incidence of CIPN following neurotoxic chemotherapy varies but has been estimated up to 68 %, being maximum within the first month after treatment and decreasing over time (Seretny et al., 2014). CIPN is only partially reversible, can have long-lasting effects and is associated with increased physical disability, falls, and significantly impaired quality of life (QoL) (Mols et al., 2013; Kolb et al., 2016; Winters-Stone et al., 2017). CIPN can act as limiting factor for chemotherapy, causing treatment delay, dose reduction or even discontinuation of therapy, thus potentially affecting the treatment outcome and increasing cancer mortality (Gewandter et al., 2020).

Several drugs have been tested in CIPN either as disease-modifiers or symptomatic agents, but effective strategies are lacking (Cavaletti et al., 2019; Loprinzi et al., 2020a,b). Drugs used to treat neuropathic pain have been explored in CIPN, but only duloxetine was reported to yield some pain relief in peripheral neurotoxicity with consistent side effects and high dropout rate (Smith et al., 2013; Avan et al., 2015; Chu et al., 2015). The heterogeneity of the pathogenetic mechanisms may be a major issue hampering effective pharmacological strategies for CIPN (Argyriou et al., 2020).

Rehabilitation, physical therapy, and other related non- pharmacological therapeutical approaches have been explored for CIPN. However, recent clinical guidelines could not form recommendations for the utility of non-pharmacologic therapies for CIPN (Loprinzi et al., 2020) or highlighted gaps in evidence (Jordan et al., 2020). Exercise was demonstrated to prevent paclitaxel-induced peripheral neuropathy in a mouse model (Park et al., 2015). Clinical studies on exercise yielded some promising results in CIPN especially for balance and fitness outcomes, although empirical evidence on its efficacy is still insufficient (Kanzawa-Lee et al., 2020; Lin et al., 2021).

The goal of this paper is to add to the expanding field of non- pharmacological treatments for CIPN with a view to form evidence- based recommendations to guide future studies. To this aim, we systematically reviewed data on rehabilitation, exercise, physical therapy, and related non-pharmacological interventions, graded the quality of evidence and offered evidence-based recommendations, and a roadmap for future studies for CIPN prevention and treatment.

2. Methods

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Moher et al., 2015; Page et al., 2021).

2.1. Eligibility criteria

Inclusion criteria were studies assessing the effect of rehabilitation, exercise, physical therapy, and other physical non-pharmacological therapies on adult cancer patients with established CIPN or receiving neurotoxic chemotherapy, published in English, and controlled with any comparator group. Our review was focused on exercise, rehabilitation and physical interventions and we excluded studies on acupuncture, invasive electrical stimulation, herbal medicine, natural products, dietetic interventions, and psychological interventions. Case reports/series, reviews, commentaries, abstracts, conference papers, studies on animal models or healthy subjects were excluded, as were studies without therapeutic goals. Table 1 reports inclusion criteria according to the PICOS model.

2.2. Search strategy

PubMed, Web of Science and CINAHL databases were searched on December 1st, 2020 for peer-reviewed papers published from database inception until October 31st, 2020 with the search string: “(Paclitaxel OR docetaxel OR taxane OR oxaliplatin OR cisplatin OR platinum OR vincristine OR vinca OR vinblastine OR thalidomide OR lenalidomide OR pomalidomide OR bortezomib OR ixazomib OR carfilzomib OR ixabepilone OR cabazitaxel OR eribulin OR carboplatin OR chemotherapy*) AND (chemotherapy induced peripheral neuropathy OR CIPN OR neuropath* OR neurotoxic* OR neuropathic pain OR neuralgia OR peripheral neuropathy OR peripheral nervous system diseases) AND (exercise OR rehabilitation OR physical activity OR physical therapy OR physiotherapy OR sensorimotor training OR strength training OR balance training OR gait training OR proprioceptive training OR electrical stimulation OR device).” The search was updated on June 2, 2021 for papers published until May 31st, 2021.

2.3. Study selection

Search results were uploaded to Rayyan (Ouzzani et al., 2016). Two authors (MH, EM) independently screened titles and abstracts. The reference lists of relevant papers were manually checked to identify additional studies potentially missed in the databases search. Any disagreement was solved by consensus or consulting a third reviewer (ST).

2.4. Data collection and analysis

A standardized data extraction sheet was utilized to collect data in a uniform manner. Two authors (MH, EM) independently extracted the following data: study design, population, CIPN severity, cancer type, chemotherapy agent, type of study (prevention in patients receiving neurotoxic chemotherapy, treatment in patients with CIPN), active intervention, comparator, outcome measures, follow-up duration, type of analysis (intention-to-treat, ITT; per protocol), results. All CIPN, pain, gait, balance, upper-limb function, fatigue,

physical function, disability, QoL, psychological status outcome measures were extracted and considered eligible. No restrictions were placed on the number of outcomes timepoints.

A meta-analysis was not feasible due to the small number of studies, the variety of active and control conditions, as well as outcomes, and the design heterogeneity of the included studies.

2.5. Risk of bias

Risk of bias was assessed independently by two authors (EM, ST) using the revised tool for Risk of Bias in randomized trials (RoB 2.0) (Sterne et al., 2019). Any disagreement was planned to be solved via consensus or by consulting a third author (MH). Risk of bias was classified as “low”, “some concerns”, or “high”.

2.6. Levels of evidence

The level of evidence and grading of recommendations were based on the Oxford Centre for Evidence-Based Medicine framework (Oxford Centre for Evidence-Based Medicine Levels of Evidence Working Group (OECBM, 2009).

3. Results

3.1. Identification and selection of the studies

Literature search identified 2791 records. After duplicates removal, 2212 papers were screened through title and abstract and 61 papers were obtained for full-text screening. Eleven additional papers were retrieved from citation searching. Two authors (MH, EM) independently in-depth examined the selected 72 papers. Disagreement concerned 2 papers (inter-raters’ agreement: 97.0 %) and was resolved by consulting a third reviewer (ST). Forty-one articles fulfilled the inclusion criteria and were included in the systematic review (Supplementary Fig. 1). The included studies were heterogeneous in terms of cancer type (mostly breast cancer), chemotherapy agents, CIPN severity at baseline, and follow-up. The retrieved studies were grouped according to the study (prevention, treatment) and intervention type (Table 2).

3.2. Risk of bias

All the included studies showed a high risk of bias (Fig. 1) due to multiple methodological issues, most commonly outcome measurement and selection of the reported result. Overall, sample size was small (median: N = 34 patients, N < 50 in 25/41 studies) and ITT analysis was lacking in 26/41 reports.

3.3. Prevention studies

Twenty-one studies were included (Table 3).

3.3.1. Exercise, endurance, and strength training—Seven studies (patients completing study: active, N = 305; control, N = 284; sample sizes: N = 27− 420) were included.

A randomized controlled trial (RCT) tested a combined treatment protocol, including endurance, strength and breathing training, in patients with advanced lung cancer receiving palliative platinum-based chemotherapy, and found significant improvement in activities of daily life (ADL), QoL, aerobic capacity and endurance, stair walking, strength, dyspnea during submaximal walking compared to conventional physiotherapy (Henke et al., 2014).

A RCT on patients under paclitaxel chemotherapy found significantly better postural stability, balance and strength to an intervention combining regular physical training and sensorimotor exercise compared to controls, who were provided with education about physical activity (Vollmers et al., 2018).

A RCT on patients under platinum-based palliative chemotherapy reported that 8-week supervised exercise program significantly improved endurance and balance and reduced neuropathic pain compared to control group that received standard recommendations to obtain physical fitness (Zimmer et al., 2018).

A proof-of-concept RCT reported less frequent CIPN symptoms, better QoL and adherence to chemotherapy to immediate compared to delayed supervised exercise during/after taxane chemotherapy (Bland et al., 2019).

A secondary analysis of a RCT found that 6-week home-based progressive walking and resistance exercise program significantly reduced CIPN sensory symptoms compared to control group, especially in older men and breast cancer patients (Kleckner et al., 2019).

A single-blind RCT found significant improvement in postural sway and lean body mass with a home-based physical activity program entailing moderate walking on patients undergoing chemotherapy vs. waiting list (Stuecher et al., 2019).

A RCT found exercise to be more effective than cold application and standard care for CIPN-related numbness in women with breast cancer (Şimşek and Demir, 2021).

3.3.2. Balance and sensorimotor training—Three studies (patients completing study: active, N = 82; control, N = 87; sample sizes: N = 48− 70) were included.

A RCT found significant improvement in balance, fitness, QoL, and significantly less CIPN signs to combined sensorimotor, endurance and strength training program over 36 weeks than standard care and physiotherapy in lymphoma and multiple myeloma patients (Streckmann et al., 2014).

A pilot single-blind trial found significant improvement of pain and sensorimotor function to home-based exercise program compared to standard care in patients with breast cancer under taxanes (Andersen Hammond et al., 2020).

A single-blind controlled study reported that lower limb balance and strengthening exercise before chemotherapy yielded significant effect on balance, QoL and pain vs. standard care, but the groups were unbalanced for chemotherapy cycle (Bahar-Ozdemir et al., 2020).

3.3.3. Massage and related techniques—Two studies (patients completing study: active, N = 41; control, N = 45; sample sizes: N = 40− 46) were included.

A quasi-randomized controlled pilot study investigated the effect of hand/foot massage aromatherapy in patients receiving oxaliplatin and reported reduction of CIPN-related pain and fatigue with active treatment (Izgu et al., 2019a).

A single-blind RCT in breast cancer patients receiving paclitaxel, reported that classical massage therapy was more effective than standard care on CIPN-related pain, QoL and some nerve conduction measures without a clear overall effect on nerve function (Izgu et al., 2019b).

3.3.4. Cryotherapy and compression therapy—Eight studies (patients completing study: N = 335; self-controlled trial: 5/8; sample sizes: N = 20− 180) were included.

A phase II self-controlled trial of compression therapy on breast cancer patients receiving Nab-paclitaxel reported that CIPN symptoms and fingertip temperature were significantly lower for the glove- protected dominant than the control non-dominant hand (Tsuyuki et al., 2016).

A pilot trial of breast cancer patients receiving paclitaxel found no significant nerve conduction changes with continuous flow thermoregulator device compared to the contralateral non-cooled side (Sundar et al., 2017).

A RCT reported no significant difference in CIPN symptoms when comparing frozen gloves/socks side to the untreated one in breast cancer patients receiving paclitaxel, but the dropout rate was very high (i.e., 76 %) due to cryotherapy discomfort (Griffiths et al., 2018).

A prospective non-randomized self-controlled trial on women with breast cancer found that incidence of objective and subjective CIPN was reduced in the dominant side using frozen gloves/socks compared to the non-dominant side (Hanai et al., 2018).

A RCT of breast cancer patients receiving paclitaxel found no significant difference on CIPN patient reported outcomes with cooling hands/feet with crushed ice vs. control group (Ruddy et al., 2019).

A RCT found no significant CIPN or QoL changes with frozen gloves on both hands vs. control in patients receiving oxaliplatin or taxanes, but one third of patients discontinued cryotherapy due to discomfort (Beijers et al., 2020).

A prospective self-controlled trial compared cold and compression therapy for the prevention of Nab-paclitaxel induced CIPN in breast cancer patients but found no difference (Kanbayashi et al., 2020).

A RCT on breast cancer patients under paclitaxel found greater reduction of CIPN incidence for the cryotherapy than the control group but only 68 % compliance (Shigematsu et al., 2020).

3.3.5. Electrical stimulation—A single RCT (N = 24 patients completing study) reported that transcutaneous electrical nerve stimulation (TENS) did not reduce CIPN occurrence vs. sham stimulation in patients undergoing oxaliplatin or paclitaxel (Tonezzer et al., 2017).

3.4. Treatment studies

Twenty studies were included (Table 4).

3.4.1. Exercise training—A quasi-experimental study (patients completing study: active, N = 51; control, N = 28; sample size: N = 79) evaluated a 2-week exercise rehabilitation program for CIPN in patients receiving oxaliplatin and found improvement of CIPN symptoms, functional test, and pain for the active vs. control group comparison (Gui et al., 2021). Of note, a consistent number of the patients (i.e., 32/79) exercised regularly before study, and most of them (i.e., 27/32) asked to join the active group.

3.4.2. Balance and sensorimotor training—Four studies (patients completing study: active, N = 65; control, N = 71; sample sizes: N = 22− 45) were included.

A pilot single-blind RCT found significantly greater improvement of postural control to 4-week interactive motor adaptation balance training program based on wearable sensors than standard care in older patients with moderate-to-severe CIPN (Schwenk et al., 2016).

A RCT compared 12-week endurance and balance training protocol to endurance training in patients with CIPN and reported significant reduction in sensory symptoms in both groups, and improved functional status in the active group only, but the ITT analysis documented no significant results (Knei et al., 2019).

A four-arms RCT explored two protocols, namely sensorimotor and whole-body vibration training compared to two control groups in patients with CIPN and found significant improvement in neuropathic pain and CIPN severity with the active compared to the control arm (Streckmann et al., 2019).

A RCT found significant neuropathic pain reduction and QoL improvement to 10-week home-based muscle strength and balance exercise program compared to standard care in patients with CIPN (Dhawan et al., 2020).

3.4.3. Neurofeedback—Two separate publications (patients completing the study: active, N = 23; control, N = 28; total sample size: N = 71) reported a RCT, where 20 sessions of neurofeedback were found to reduce CIPN-related pain severity and impact compared to waiting list (Prinsloo et al., 2017), and 4-month follow-up showed better QoL and less fatigue in the active group (Prinsloo et al., 2018).

3.4.4. Massage and related techniques—Three studies (patients completing study: active, N = 86; control, N = 85; sample sizes: N = 48− 96) were included.

A quasi-experimental study reported significant foot skin temperature increase and QoL improvement to foot bathing vs. massage in CIPN patients; however, there was no control/sham group (Park and Park, 2015).

A RCT found no significant difference to 6-week reflexology program vs. standard care in patients with grade 2− 4 CIPN (Kurt and Can, 2018).

A RCT reported that aroma self-foot reflexology was significantly more effective on CIPN symptoms, ADL, anxiety, and depression than control group, which received treatment 6 weeks later (Noh and Park, 2019).

3.4.5. Electrical stimulation—Four studies (patients completing study: active, N = 99; control, N = 100; sample sizes: N = 35− 72) were included.

A phase II RCT found greater reduction of CIPN severity to scrambler therapy than TENS (Loprinzi et al., 2020b).

A pilot phase II RCT reported no difference between real and sham scrambler treatment in terms of reduction of CIPN-related pain (Smith et al., 2020).

A RCT found significant improvement for cold arthralgia only to real vs. sham low-frequency electrostimulation in patients with CIPN receiving duloxetine or pregabalin (Song et al., 2020).

A pilot cross-over RCT found non-significant difference between scrambler therapy and TENS (Childs et al., 2021).

3.4.6. Other physical interventions—Six studies (patients completing study: active, N = 150; control, N = 152; sample sizes: N = 31− 131) were included.

A four-arm pilot RCT found no difference between three complementary approaches (i.e., Reiki, yoga, meditation) and holistic education only (control arm) (Clark et al., 2012).

A RCT found improved one-legged stance test and reduced feet discomfort to 12-week interferential therapy and high-power (active), but no significant difference was found vs. low-power long-wave diathermy (control) in chronic CIPN patients (Lindblad et al., 2016).

A RCT found no significant difference between photobiomodulation with/without physiotherapy for CIPN symptoms (Argenta et al., 2017).

A RCT reported very slight significant improvement of nerve conduction velocity, but no effect on other outcomes, to magnetic field therapy vs. sham for grade 1− 4 CIPN (Rick et al., 2017).

A pilot RCT found no significant differences for whole-body vibration associated to an integrated program (massage, passive mobilization, physical exercise) than integrated program only in grade 2− 3 CIPN patients (Schönsteiner et al., 2017).

A pilot RCT reported significant improvement in pain and sensory CIPN symptoms to low-intensity ultrasound than standard care at the end of treatment, but no between-group difference at 6-week follow-up (Al Onazi et al., 2021).

4. Discussion

We provide a comprehensive systematic review on exercise, rehabilitation, physical therapy, and related non-pharmacological interventions for CIPN. We included 41 articles, with heterogenous cancer types, chemotherapy compounds, study outcomes and study design. Some studies focused on preventive interventions (N = 21) and the others used therapeutic interventions in established CIPN (N = 20).

We found seven prevention studies on exercise, endurance, and strength training in patients with various cancer types, mostly treated with taxane, platinum compounds, their combination, or vinca alkaloids, and one therapeutic study on exercise training (Gui et al., 2021). Four papers (Vollmers et al., 2018; Zimmer et al., 2018; Bland et al., 2019; Şimşek and Demir, 2021) explored mixed protocols, where more than one intervention was applied. Physical activity during chemotherapy may successfully prevent strength loss, improve balance, slow-down CIPN development and stabilize patient's function. Because of improved postural stability and strength, cancer patients undergoing multimodal physical training during chemotherapy may be less liable to falls and fall-related injuries. Our findings are in keeping with previously published systematic reviews and meta-analyses on exercise to prevent CIPN (Kanzawa-Lee et al., 2020; Lin et al., 2021; Tanay et al., 2021; Kleckner et al., 2021) and to improve established CIPN symptoms, with positive effects on functional outcomes and QoL (Duregon et al., 2018). Nonetheless, these apparently promising results should be cautiously considered, because of several potential confounders. First, cancer type and severity, and chemotherapeutic compounds differed across studies. Second, methodological differences, including intervention design (type of activities, length, intensity), assessment time, and outcome measures may hamper the findings replication (Kanzawa-Lee et al., 2020; Lin et al., 2021; Duregon et al., 2018; Park et al., 2021). Third, many enrolled patients had stage III/IV cancer (Henke et al., 2014; Zimmer et al., 2018; Stuecher et al., 2019), most likely presenting generalized fatigue and cancer-related cachexia that complicate interpretation of the results. Fourth, the effect of pre-treatment level of patients' physical activity is not always adequately addressed in therapeutic studies (Gui et al., 2021). Despite these considerations, there is moderate quality evidence on physical activity-based interventions to prevent CIPN escalation during chemotherapy thereby maintaining the functional autonomy of patients, and preliminary evidence for established CIPN symptoms.

Three prevention studies reported that balance and sensorimotor training may reduce the risk of pain, muscle, balance, and fitness impairment (Streckmann et al., 2014; Bahar-Ozdemir et al., 2020; Andersen Hammond et al., 2020), but reduced CIPN rate in the intervention group was reported by a single study (Streckmann et al., 2014). Subjective CIPN outcome measures were used in most studies (Streckmann et al., 2014; Bahar-Ozdemir et al., 2020), thus not offering full support to a neuroprotective role of these approaches and being potentially affected by placebo effect, in the absence of objective measures. Moreover,

studies were not balanced in terms of pre-treatment physical activity, which may represent a potential confounder. Treatment studies on balance and sensorimotor training with supervised exercise (Kneis et al., 2019; Streckmann et al., 2019), home-based training (Dhawan et al., 2020), and an interactive program based on wearable sensors (Schwenk et al., 2016) reported improvement in sensory symptoms, neuropathic pain, balance, postural control, and QoL. Exercise types differed across the studies that shared balance training as a common feature. One study with small sample size (N = 40) suggested balance exercise to be more effective on CIPN symptoms than whole body vibration (Streckmann et al., 2019). Based on this evidence, and in line with a previous systematic review (Kanzawa-Lee et al., 2020), balance and sensorimotor training could be included in CIPN rehabilitation protocols, but there is not enough evidence supporting a specific training protocol.

Two reports from the same group explored short- and long-term effects of neurofeedback and found improvement of pain, QoL and fatigue in CIPN patients, mainly breast cancer survivors treated with taxanes (Prinsloo et al., 2017, 2018). Although neurofeedback may represent an interesting CIPN treatment strategy, with possible home-based administration, these data should be considered as very preliminary, given the waitlist control condition, and the small number of patients completing the study (N = 41).

Two CIPN prevention studies on massage and related techniques reported slight reduction of neuropathic pain, subjective symptoms, fatigue and QoL, but had small sample size (N = 40− 46), lacked a placebo/sham arm and long-term follow-up (Izgu et al., 2019a,b). Three therapeutic studies using foot bathing, foot massage, reflexology, and aroma-reflexology reported mild improvement of sensory CIPN symptoms, but variable effect on ADL and QoL (Park and Park, 2015; Kurt and Can, 2018; Noh and Park, 2019). The body of research on massage and related therapies for CIPN is limited, and the studies lacked long-term follow-up, appropriate control group, and used different outcome measures that makes comparing and applying their results difficult. Since massage and related techniques showed no adverse effects, they can be considered in CIPN non-pharmacological approach, although without established evidence.

Cryotherapy and compression therapy reduce blood flow to fingers or toes during chemotherapy using cold gloves or stockings (−25 °C to− 4 °C) or compression gloves. We found six cryotherapy prevention studies, with significant changes to active treatment reported in two, negative findings in three and significant changes to single CIPN scale items but not the overall score in one. A major issue is that three studies (Sundar et al., 2017; Griffiths et al., 2018; Hanai et al., 2018) used the same patient as an internal control by comparing treated vs. non-treated side, instead of an independent control group. A study found no significant difference between cryotherapy and compression therapy (Kanbayashi et al., 2020). A study reported reduced CIPN rate in the treated vs. untreated side with compression therapy (Tsuyuki et al., 2016). Strengths of these studies include often large effect sizes and multiple CIPN outcomes (patient reported, clinical tests). Limitations include lack of phase III RCTs and few studies using traditional patient-level randomization. In accordance with a previous review (Bailey et al., 2021), evidence on the role of cryotherapy for CIPN prevention is not conclusive, with some compliance concerns because of the high drop-out rate. Compression therapy may be better than cryotherapy

being logistically easier and less expensive, however there is insufficient evidence to support its use without further studies.

Five studies explored electrical stimulation. A RCT reported that real TENS was not better than sham TENS for CIPN prevention (Tonezzer et al., 2017). Four therapeutic RCTs yielded mixed results, with one showing greater CIPN severity reduction with scrambler therapy vs. TENS (Loprinzi et al., 2020b), one reporting low-frequency electrostimulation in association with pharmacological intervention to reduce cold arthralgia vs. sham arm (Song et al., 2020), and two studies reporting no difference between real and sham scrambler therapy (Smith et al., 2020), and no significant difference between scrambler therapy and TENS (Childs et al., 2021). Given the low number of studies, relatively small sample sizes (N = 35− 72), contrasting findings, and methodological issues, the data on electrical stimulation should be considered as very preliminary.

Comparison of interferential therapy and high-power vs. low-power long-wave diathermy documented balance improvement to the former and pain reduction to the latter, but the absence of a sham control group impeded robust conclusions (Lindblad et al., 2016). Magnetic field therapy resulted in statistically significant but very slight improvement in peroneal nerve conduction velocity vs. placebo (Rick et al., 2017). As reduced nerve conduction velocity is not the primary neurophysiological marker of CIPN (Argyriou et al., 2019), the clinical significance of this result is unclear. Whole body vibration as part of a program including massage, stretching, and exercise (Schönsteiner et al., 2017), and reiki, yoga, meditation and photobiomodulation (Clark et al., 2012; Argenta et al., 2017) yielded no significant differences across conditions. The addition of ultrasound therapy to standard care resulted in short-term improvement of pain and sensory CIPN symptoms (Al Onazi et al., 2021). These data suggest some possible benefit of other physical therapies on CIPN, without adverse side effects, but should be considered as very preliminary.

An important issue is demonstration of a mechanistic rationale for non-pharmacologic therapies in CIPN prevention or treatment. While this is more established for exercise (Park et al., 2015), other non-pharmacologic interventions lack a clear rationale for efficacy. While non-pharmacologic therapies are often associated with better side effect profile than pharmacological treatments, there are potentially significant costs of administration and delivery, so efficacy and a strong biological rationale are two prerequisites for their prescription.

Another limitation is that, only a limited number of studies (i.e., 21/ 41) focused on QoL. Although the EORTC-QLQ was the most applied outcome measure, results between studies appear inconsistent, underscoring the need of better QoL assessment tools in CIPN studies (Park et al., 2021). The high frequency of long-lasting CIPN symptoms in cancer survivors and the association between symptoms burden and reduced QoL may influence rehabilitation outcomes, and future studies should address QoL with appropriate tools (Eikeland et al., 2021; Lauritsen et al., 2021; Park et al., 2021).

Based on the studies included above, we generated a list of recommendations for rehabilitation, exercise, and physical therapy to prevent and/or treat CIPN (Table 5). For

an example exercise prescription to treat CIPN, see Klechner et al., 2021. Most of the interventions we reviewed are biased by methodological issues, i.e., small sample size, heterogeneity in cancer types, chemotherapy compounds, intervention including combined protocols, and outcome measures, appropriate control group and short-term follow-up, as well as the timing of assessments. Therefore, a meta-analysis was not feasible. It is important to note that while previous meta-analyses have been attempted (Lin et al., 2021), the outcome measure and study design heterogeneity significantly limits the ability to draw conclusions. Accordingly, efforts to standardize outcome measure and study design elements are important to enable future meta-analyses to be conducted (Park et al., 2021). These limitations impede solid conclusions on the role of the treatments here reviewed.

This review did not cover all the non-pharmacological treatments, as it did not deal with acupuncture, herbal medicine, natural products, dietetic interventions, and psychological interventions (Brami et al., 2016).

5. Conclusions

Because of the methodological issues of included studies, only exercise, endurance, strength, balance, and sensorimotor training show some evidence (level B recommendations) (Oxford Centre for Evidence-Based Medicine Levels of Evidence Working Group (OECBM, 2009) for the prevention and treatment of CIPN, while data for other treatments is preliminary and/or inconclusive. To offer stronger evidence on this topic, we recommend future studies a) to be multicentre to provide geographical and cultural generalizability, offer rapid accrual rate and the ability to reach large-powered sample sizes required for a phase III trial, b) to recruit homogeneous populations in terms of cancer type, stage and chemotherapy compound to reduce the potential effect of these covariates and increase precision of the results, c) to include appropriate subjective and objective outcome measures to explore which CIPN features are affected, d) adequate control/sham group to reduce the placebo effect, e) ITT analysis with last observation carried forward data, e) long-term follow-up to document the effect duration, f) measures of compliance and adherence to treatment, g) dose-response studies, and h) cost-effectiveness analyses to prove the usefulness in the real-world setting. Moreover, CIPN prevention and treatment trials may have different ideal study requirements, in that demonstration of efficacy of an intervention as a preventative strategy may require larger and more homogenous samples than treatment trials. Appropriately controlled clinical trials to demonstrate efficacy of non-pharmacological interventions for the prevention/treatment of CIPN are required before definitive recommendations can be made to improve QoL in cancer survivors treated with neurotoxic chemotherapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

Stefano Tamburin, MD, PhD, is Associate Professor of Neurology at the Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona. His areas of research and clinical interest include peripheral nervous system diseases, neuropathic pain, central and peripheral neurotoxicity to chemotherapy for cancer, with an integrative and translational approach that encompasses clinical evaluation, clinical neurophysiology, imaging, rehabilitation, and applied technologies. He is Secretary of the Neuropathic Pain Consortium of the Peripheral Nerve Society and Co-Chair of the neurological complications, biomarkers and preclinical work subgroup of the Multinational Association of Supportive Care in Cancer. He authored more than 180 publications in international peer- reviewed journals (Scopus *h*-index = 32).

Susanna B. Park, PhD, is a National Health and Medical Research Council of Australia RD Wright Biomedical Research Career Development Fellow and Associate Professor in Neuroscience at the Brain and Mind Centre, University of Sydney, Australia. Dr Park leads a multidisciplinary research group investigating assessment strategies, treatments and risk factors in neuropathy and neuromuscular disease. She has expertise in multidisciplinary peripheral neuropathy research, leading several studies examining clinical translation, assessment strategies, treatment, and risk factors for chemotherapy- induced peripheral neuropathy with >115 peer-reviewed publications. She obtained her PhD from the University of New South Wales, Australia in 2010 and subsequently undertook postdoctoral training at the Institute of Neurology, University College London.

Angelo Schenone, is Full Professor at University of Genoa and Director of Neurology Unit of IRCSS San Martino Hospital and the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetic and Maternal and Infantile Sciences, University of Genoa. He is a Professor of Neurology and has expertise in the management of patients affected by acquired and hereditary neuropathies. He is the past president of Italian Society of the Peripheral Nervous System. From 2015–2019 he served as a member of the Board of the Italian Society of Neurology. He is member of Peripheral Nerve Society, Italian Society of Neurology and Italian Society of Neuropathology. Prof Schenone is the director of the residency program at the University of Genoa and Coordinator of the editorial board of the Genova University Press.

Elisa Mantovani, MSc, is a PhD student in Neuroscience, Psychological and Psychiatric Sciences, and Movement Sciences at University of Verona, Italy. She is currently working on neurological complications of cancer treatments, both at peripheral (e.g., chemotherapy induced peripheral neuropathy) and central (e.g., cancer related cognitive impairment) levels. She has authored 27 publications in international peer-reviewed journals, with an *h*-index of 5.

Mehrnaz Hamedani, is a physiotherapist, who obtained her PhD in Neuroscience from the University of Genoa. Currently, she is working as a postdoctoral fellow at the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa and IRCCS San Martino Hospital. She has expertise in

neurorehabilitation, medical devices (robotics and sensors), and their use in for motor neurorehabilitation.

Paola Alberti, MD, PhD, is a postdoctoral fellow at University of Milano-Bicocca (Monza, Italy), working on clinical/preclinical chemotherapy-induced peripheral neurotoxicity (CIPN). Her preclinical research focuses on axonal hyperexcitability. She is the PI of the International CIPN Assessment and Validation Study (ICAVS, NCT04633655), the CIPN COST study (NCT04986891) to ascertain socio-economic burden related to CIPN, and the Neuper study (NCT05088681) aiming to reverse sensory ataxia due to polyneuropathy. She is vice chair of the junior board of the Peripheral Nerve Society, co-chair of the chemotherapy-induced peripheral neurotoxicity working group of the Multinational Association of Supportive Care in Cancer and member of the Neuroscience/translational neurology panel in the European Academy of Neurology. She authored 66 publications in international peer-reviewed journals (*h*-index=27).

Vesile Yildiz-Kabak, is a physiotherapist, PhD, and post-doctoral researcher at Faculty of Physical Therapy and Rehabilitation, Hacettepe University, Turkey. Research interests include functional evaluations of cancer patients, exercise, rehabilitation, physical therapy for cancer patients, cancer related side effects including neuromuscular ones, fatigue, and pain.

Ian R. Kleckner, PhD MPH is Associate Professor and Director of the Cancer Control Mind & Body Lab at the University of Maryland Baltimore School of Nursing. He and his lab study how cancer chemotherapy causes side-effects such as neuropathy and distress, and how to treat these symptoms using exercise assessed via randomized clinical trials. He uses methods from psychophysiology (measuring heartbeats, skin conductance), neuroimaging (fMRI), exercise science, and psychological and behavioral science with computational approaches honed from his backgrounds in physics and biophysics. He is PI of four NIH/NCI grants (K07, R21s, NCORP) including a nationwide clinical trial of exercise for CIPN in the US. He has published nearly 50 scientific papers and received numerous awards for his working including the Best of American Society for Clinical Oncology (ASCO). For more information see www.iankleckner.com or Twitter @iankleckner.

Noah Kolb, MD is Associate Professor of Neurological Sciences and the Robert Larner College of Medicine at the University of Vermont. Clinically, he cares for neuromuscular patients, performs EMGs and is the Associate Director of the Muscular Dystrophy Association Clinic at UVM. He is the clerkship director of the Neurology Clerkship and Acting Internship for medical students at UVM. His research focuses on multiple aspects of chemotherapy induced peripheral neuropathy and he is the PI of a National Cancer Institute funded multicenter randomized controlled trial investigating a new care model for patients with CIPN.

Miryam Mazzucchelli, MD, is a Physical and Rehabilitation Medicine Physician with expertise in in neurological and cognitive rehabilitation. She is a PhD student in Neuroscience at University of Milano Bicocca with a research project on rehabilitation in peripheral neuropathies and motor control (NEUPER study).

Brendan L. McNeish, MD, is currently a neuromuscular medicine fellow at the University of Vermont. He has a clinical and research interest in understanding the impact of neuromuscular and neurocognitive impairments of cancer and its treatment on mobility in cancer survivors.

Andreas A. Argyriou, MD, PhD, serves as Senior Consultant Neurologist and Neurophysiologist at the Saint Andrew's General Hospital of Patras, Greece, and Senior Research Fellow at the Laboratory of Clinical Oncology, Division of Clinical Oncology, Department of Medicine, University Hospital of Patras, Greece. He is Board Member (2018-today) in the Toxic Neuropathy Consortium of the Peripheral Nerve Society and coordinator of the corresponding Clinical Working Group. He is also Co-Chair (2020-today) of the chemotherapy-induced peripheral neurotoxicity subgroup of the Multinational Association of Supportive Care in Cancer. Dr. Argyriou authored more than 160 publications in international peer-reviewed journals, currently obtaining more than 5000 citations and an *h*-index of 35.

Guido Cavaletti, MD, PhD, is Professor of Human Anatomy, School of Medicine and Surgery, University of Milano-Bicocca, senior consultant neurologist and head of the outpatient clinic at the Department of Neurology, S. Gerardo University Hospital, Monza, Italy. He is Vice-Rector for Research and Head of the Experimental Neurology Unit, University of Milano-Bicocca. He served as Member of the Board of Directors of the Peripheral Nerve Society and as President of the Italian Peripheral Neuropathy Association. He is currently the Chair of the Toxic Neuropathy Consortium of the Peripheral Nerve Society. Prof. Cavaletti gave lectures on the peripheral neurotoxicity of anticancer drugs at American Academy of Neurology, American Society for Clinical Oncology and European Society for Medical Oncology meetings, as well as at FDA and EMA boards on toxic neuropathies and trials design. Author of more than 300 full papers in international peer-reviewed journals (Scopus *h*-index = 64).

Ahmet Hoke, MD, PhD, is Professor of Neurology and Neuroscience, Director of the Daniel B. Drachman Division of Neuromuscular Diseases and Director of the Merkin Peripheral Neuropathy and Nerve Regeneration Center at Johns Hopkins University School of Medicine. Dr. Hoke's clinical practice focuses on peripheral neuropathies and nerve injuries. His research interest includes studies on biology of peripheral axons and Schwann cells and disorders affecting the peripheral nervous system. He is the recipient of several awards including Derek Denny Brown Young Neurological Scholar Award (2005) and Wolfe Neuropathy Research prize (2018) given by the American Neurological Association, Myung Memorial Lecture Award (2017) by the Korean Neurological Association and Nejat Eczacibasi Medical Scientist Award (2019) by the Eczacibasi Foundation, Turkey. He is on the Board of Directors of Peripheral Nerve Society and Vice-President of the Toxic Neuropathy Consortium. He serves on several editorial boards and is the Editor-in-Chief of Experimental Neurology and Associate Editor for Annals of Clinical and Translational Neurology.

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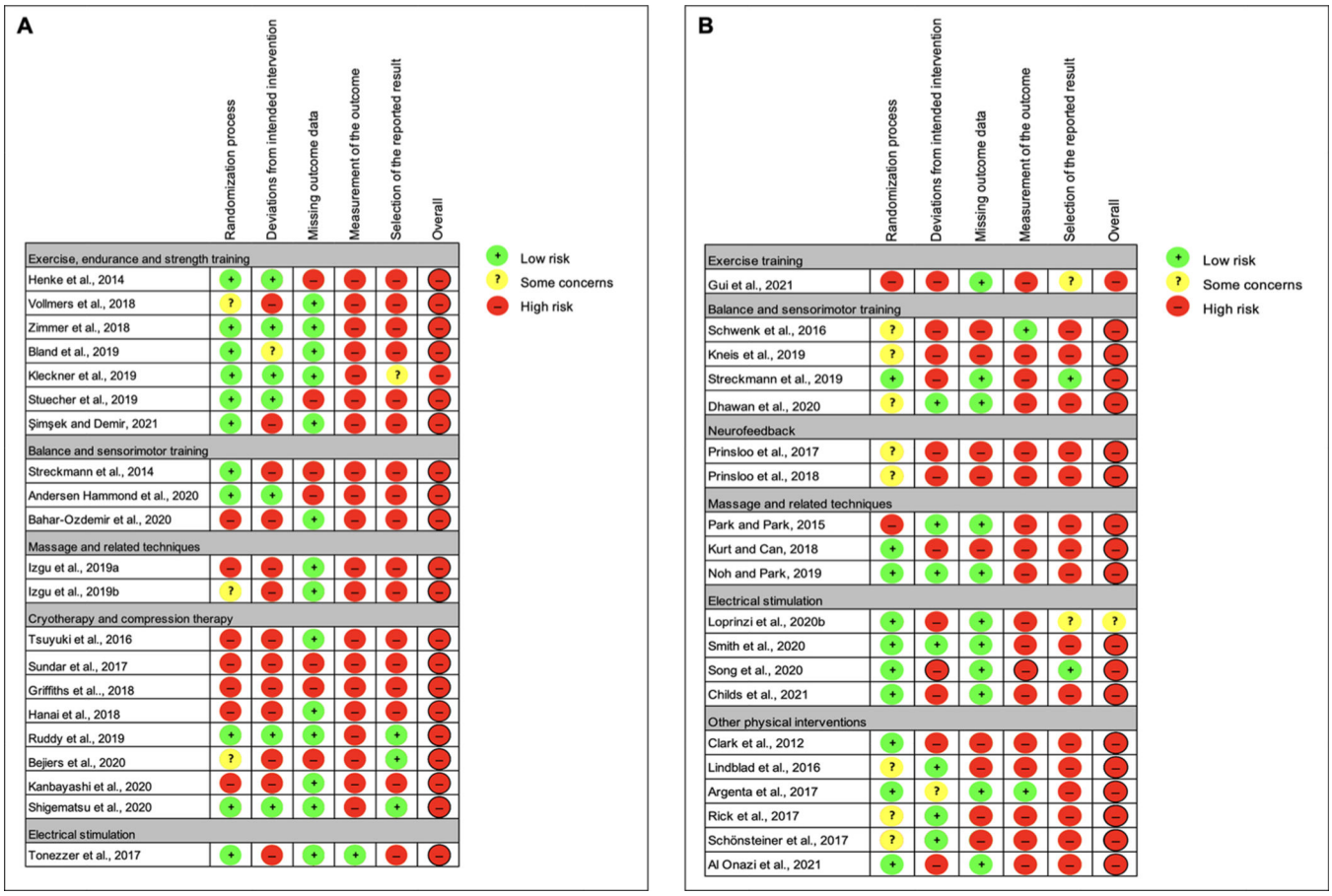

Fig. 1.

Assessment of the risk of bias according to the RoB 2.0 tool for the prevention (panel A) and therapeutic studies (panel B) included in the systematic review.

Table 1

Inclusion criteria according to the PICOS model.

Criterion	Description
Participants	Patients with cancer with CIPN or receiving neurotoxic chemotherapy
Intervention	Rehabilitation, exercise, endurance, strength, balance, gait, sensorimotor, or proprioceptive training, neurofeedback, massage and related techniques, cryotherapy, compression therapy, electrical stimulation, other physical therapies
Comparator	Any comparator group, i.e., sham, standard treatment, waiting list, active treatment
Outcome	All measures/outcomes applied to CIPN and/or rehabilitation, including outcomes related to peripheral neuropathy, pain, gait and balance, fatigue, physical functioning, disability, quality of life, psychological status, body composition, fidelity/adherence to treatment
Study design	Controlled studies with any type of comparator

CIPN: chemotherapy-induced peripheral neuropathy.

Table 2

The main types of interventions for CIPN prevention and treatment reviewed here.

Intervention	Definition
Endurance training	Aerobic exercise including activities aimed at improving and maintaining the fitness of the cardiovascular system
Strength training	Anaerobic activity including exercise aimed at inducing muscular contraction to increase the strength, anaerobic endurance, and size of skeletal muscles
Balance and sensorimotor training	Associative training in which observation of one action is systematically paired with performance of another action It includes vestibular, visual and oculomotor activities, cervical neuromotor control and strength training, postural/balance exercises
Neurofeedback	Learning intervention where a patient is given a reward via auditory and/or visual stimuli when voluntary changes are made in brain activity within a designated region
Massage	Manipulation of the body's soft tissues to reduce pain and improve well-being
Reflexology	The application of pressure to areas on the feet/hands to improve well-being
Aromatherapy	Alternative/complementary therapy that uses essential oils and other aromatic plant compounds to improve well-being
Cryotherapy	Therapeutic regional hypothermia reached by means of frozen gloves/socks to decrease microvascular flow in the hands/feet
Compression therapy	Wearing stockings and sleeves for 24 h to decrease microvascular flow in the hands/feet
TENS and electrostimulation	The application of low voltage electrical current stimulation to improve pain through peripheral and central nervous mechanisms
Scrambler therapy	A type of electrical stimulation technique meant to reduce pain input with non-painful stimulation
Interferential therapy	Electrophysical method based on the application of an electric field in the painful area via four electrodes or vacuum cups that are placed on the skin
Long wave diathermy	Electrical current therapy involving generation of oscillating electromagnetic fields to produce heat deep inside a targeted tissue
Photobiomodulation	Light therapy using non-ionizing, low power, laser light sources
Whole-body vibration	Vibrating platform that transmits a vibration stimulus from the feet to the body and generates a vertical oscillation
Reiki, yoga and meditation	Alternative medicine therapies to improve well-being

CIPN: chemotherapy-induced peripheral neuropathy. TENS: transcutaneous electrical nerve stimulation.

Table 3

Results of prevention studies for CIPN.

Ref	Study design	Population	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
Exercise, endurance, and strength training (Included, N = 700; completed the study, N = 589; active intervention, N = 305; control group, N = 284; sample size: N = 27—420)											
Henke et al., 2014	RCT	N: 46 (M/W: NS; age ≥ 18)	Lung (stage III-IV)	Platinum	Endurance, strength and breathing techniques (5 day/week for endurance and breathing, 2 day/ week for strength; N: 18 completed the study)	Conventional physiotherapy (N: 11 completed the study)	ADL (Barthel Index); QoL (EORTC QLQ-C30); endurance capacity and dyspnea perception (6MWT, stair walking, modified Borg Scale, muscle strength)	No	Per protocol analysis (29/46, 63 % patients completed the trial)	Improvement in Barthel Index, EORTC QLQ-C30, 6MWT, stair walking, muscle strength and reduction of modified Borg Scale in active vs. control group	2B
Vollmers et al., 2018 *	RCT	N: 43 women; age: 50.5 ± 11.1	Breast	Paclitaxel	Regular physical training and sensorimotor exercise (2 sessions/week during chemotherapy and for 6 weeks thereafter; N: 17 completed the study)	Suggestion of physical activity designed autonomously (N: 19 completed the study)	Sway areas (posturometry); postural stability (FAB); upper extremity strength (hand dynamometer); lower extremity strength (CRT); QoL (EORTC QLQ-C30); symptoms questionnaires (EORTC QLQ-BR23, EORTC QLQ- CIPN20, MFI-20)	6 weeks after chemotherapy	Per protocol analysis (36/43, 84 % patients completed the trial)	Postural stability, FAB and strength better in the experimental than control group	2B
Zimmer et al., 2018 *	RCT	N: 30 (M: 21, W: 9; age: 50–81)	Colorectal (stage IV)	Platinum	Supervised exercise program (endurance, resistance, balance training; 60 min, 2/week, 8 weeks; N:	Written standard recommendations to obtain physical fitness (N: 9/13 completed the study)	Neuropathic symptoms (FACT/ GOG-Ntx); endurance capacity (6MWT), strength (h1RM) and	4 weeks	24/30 (75 %) patients completed the study; ITT analysis	Intervention significantly improved strength and balance function; neuropathic symptoms stable over	2B

Ref	Study design	Population	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
					15/17 completed the study)		balance (GGT-Reha)			time to intervention, while they worsened in the control group	
Bland et al., 2019 *	RCT	N: 27 women; age: 50.2 ± 10.2	Breast	Taxane	Immediate exercise (supervised aerobic, resistance, balance training; 3 days/week for 8–12 weeks) during chemotherapy (N: 12)	Delayed exercise (same protocol as active intervention but started, 2—3 weeks after the last chemotherapy (N: 15)	CIPN symptoms (EORTC QLQ-CIPN20) and QoL (EORTC QLQ-C30); lower limb vibration sense and pinprick	10—15 weeks after chemotherapy	Per protocol analysis (27/31, 87 % patients completed the trial)	Patients who reported moderate to severe toes/ feet numbness and impaired vibration sense was smaller and quality of life was higher in immediate exercise group	1B
Kleckner et al., 2019	Multicenter RCT	N: 420, of whom 355 (M: 36, W: 329; age: 56 ± 11) completed the study	Breast, lymphoma, colon, lung, other	Taxane, platinum, vinca alkaloid	Exercise for Cancer Patients (EXCAP©®): a home-based progressive walking and resistance exercise (six-week; N: 170/ 231 completed the study)	Standard care, no exercise (N: 185/ 225 completed the study)	CIPN symptoms (numbness, tingling, hot/ coldness in hands/feet)	No	85 % patients completed the trial; ITT analysis	Exercise reduced CIPN symptoms and was more effective in older patients, men and patients with breast cancer	1B
Stuecher et al., 2019	Single-blind RCT	N: 44 (M:25, W: 19; age: 67.1 ± 7.8)	Gastrointestinal (UICC stage III- IV)	NS	Home-based physical activity program (moderate walking 150 min/ week; N: 13/22 completed the study)	Waiting list (N: 15/ 22 completed the study)	ADL relevant physical performance (SPPB: gait speed, balance, lower extremity muscle strength); postural sway; proprioception (Rydel-Seiffer tuning fork); dietary behavior (MNA); body	12 weeks after chemotherapy	Per protocol analysis (28/44, 64 % patients completed the trial)	Postural sway and lean body mass improved for exercise vs control group	2B

Ref	Study design	Population	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
							composition (BIA)				
Şimşek and Demir, 2021	RCT	N: 90 women (age: 20 - ≥ 60)	Breast (stage II- IV)	Taxane	Cold application (15 min before and 15 min after chemotherapy over 12 weeks; N: 30); exercise (at home strength, balance, stretching, 15–30 min/ session, 5 sessions/week over 12 weeks; N: 30)	Standard care (N: 30)	CIPN symptoms and intensity (CIPN assessment tool)	No	ITT analysis	Exercise was more effective than cold application and standard care in reducing CIPN related numbness in hands and feet	2B
Balance and senso rimotor training (Included, N = 186; completed the study, N = 169; active intervention, N = 82; control group, N = 87; sample size: N = 48—70)											
Streckmann et al., 2014 *	RCT	N: 56 (M: 42, W: 14; intervention group, age: 44, range: 20–67; control group, age: 48, range: 19–73)	Non-Hodgkin lymphoma B/T, Hodgkin lymphoma, multiple myeloma	NS	Aerobic endurance, sensorimotor and strength training (60 min/session, 2 days/week, 36 weeks; N: 26/28 completed the study)	Standard care and physiotherapy (N: 25/28 completed the study)	QoL (EORTC QLQ- C30); proprioception (tuning fork); balance (cumulative sway paths, peak-to- peak amplitude, time needed to regain balance control, number of failed attempts); fitness (incremental step test); side effects (SGA, HADS, FEDA)	No	ITT and per protocol analysis (51/56, 91 % patients completed the trial)	Increase in balance and fitness measures, QoL scores; reduced incidence of peripheral neuropathy in active vs. control group; mean compliance: 65%	2B
Andersen Hammond et al., 2020	Pilot singleblind RCT	N: 48 women (age: 54.5 ± 10)	Breast (stage I-III)	Taxane	Physical therapy (home exercise; mean: 8.3 months; N: 22)	Standard care (no exercise or appointment with a physical therapist; N: 26)	Pain (NRS, S-LANSS); DASH; vibratory threshold; pain pressure threshold; hand	6 months after chemotherapy	Per protocol analysis (48/60, 80 % patients completed the trial)	Pain decreased over time, pain pressure threshold and grip dynamometry improved in	

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Ref	Study design	Population	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
							dynamometry grip			the active treatment group; participants reporting exercise had preservation of vibration and normal heat pain thresholds vs. more sedentary ones	
Bahar-Ozdemir et al., 2020 *	Single-blind controlled prospective study	N: 70, of whom 60 (M: 29, W:31; age: 52.9 ± 11.1) completed the study	Colorectal, lung, breast	Paclitaxel, oxaliplatin, cisplatin, paclitaxel and carboplatin, bortezomib, vincristine	Lower limb balance and strengthening exercise (20 min/ session, 5 days/ week, 10 weeks; N: 24/33 before chemotherapy)	Standard care (N:36/37 after three cycles of chemotherapy)	Balance measures (BBS, mCTSIB, US, LOS, STS); neuropathic pain (Pain DETECT); QoL (EORTC QLQ-C30)	No	Per protocol analysis (60/70, 86 % patients completed the trial)	Increase in balance measure and QoL scores and reduction of Pain DETECT in active vs. control group (groups were unbalanced/ unmatched for chemotherapy cycle)	3B
Massage and related techniques (Included, N = 86; completed the study, N = 86; active intervention, N = 41; control group, N = 45; sample size: N = 40—46)											
Izgu et al., 2019a	Open label pilot quasi RCT	N: 46 (M: 27, W: 19; age: 55.8 ± 8)	Colorectal, Gastric	Oxaliplatin	Aromatherapy hand and foot massage (3 sessions/week, weeks 1—6, 18 sessions total, 10 min/ hand or foot, total 40 min; N: 22)	Standard medical care (N: 24)	Patient questionnaire; painful parestesia (NRS); neuropathic pain (DN4); PFS.	2 weeks	ITT analysis	Reduced neuropathic pain rate and painful paresthesia in the active than comparator group; reduced fatigue severity at follow- up in the active than comparator group	2B

Ref	Study design	Population	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
Izgu et al., 2019b	Single-blind RCT	N: 40 women (age: 45.8 ± 10.1)	Breast	Paclitaxel	Classical massage (30 min/session, once/week, 12 weeks; N: 19)	Standard care (N: 21)	Neuropathic pain (S-LANSS); QoL (EORTC QLQ-CIPN20); NCS measures (SNAP, CMAP)	16 weeks	ITT analysis	Reduced S-LANSS, increased EORTC QLQ-CIPN20 and median SNAP amplitude in massage than control group	2B
Cryotherapy and compression therapy (Included, N = 425; completed the study, N = 335; sample size: N = 20—180)											
Tsuyuki et al., 2016	Phase II multicentre, selfcontrolled trial	N: 42 women (median age: 60, range: 35–74)	Breast	Nab-paclitaxel	Surgical glove (one size smaller than the tight-fitting size, 30 min before, 30 min during and 30 min after nab-paclitaxel infusion)	No surgical glove on the non-dominant hand	CIPN symptoms (CTCAE v 4.0 ≥ 2); PNQ; fingertip temperature	No	ITT analysis	Reduced rate of CIPN (CTCAE v 4.0 ≥ 2) for surgical glove vs. control hand, reduced prepost fingertip temperature	2C
Sundar et al., 2017	Prospective Internally controlled pilot trial	N: 20 women (mean age: 53, range: 32–67)	Breast	Paclitaxel	Continuous-flow limb hypothermia sessions (3 h during paclitaxel infusion)	Non-cooled limb	Tolerance to limb hypothermia (VAS, subjective tolerance scale, shivering assessment scale); neuropathy (NCS, TNS)	3 months afte chemotherapy	Per protocol analysis (17/20, 85% patients completed the trial)	No significant difference between treated and untreated side	2B
Griffiths et al., 2018	RCT	N: 29 women (mean age: 47.3, range: 35–68)	Breast	Paclitaxel	Frozen glove and sock on either dominant or nondominant side (210 min)	No frozen glove/ sock on the other side	Neuropathic pain (NPSI); pain severity (BPI); sensory sensitivity (QST)	2 weeks	Per protocol analysis (7/ 29, 24 % patients completed the trial)	No significant difference between treated and untreated side	2C
Hanai et al., 2018	Prospective self controlled trial	N: 40 women (age: 56.0 ± 13.8)	Breast	Paclitaxel	Frozen glove and sock on the dominant side (90 min)	No frozen glove/ sock on the nondominant side	Tactile (Semmes-Weinstein monofilament test), thermal	No	Per protocol analysis (36/40, 90 %	Reduction of tactile and thermal deficit, PNQ scores,	2C

Ref	Study design	Population	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
							(thermal stimulator) and vibration (tuning fork) sensation; dexterity (Grooved Pegboard Test); subjective symptoms (PNQ); NCS (NCV, CMAP)		patients completed the trial)	deterioration of dexterity on the intervention (hands, feet) vs. control side	
Ruddy et al., 2019	Prospective randomized pilot trial	N: 42 (M: 1, W: 41; age: 53.5 ± 4.1)	Breast	Paclitaxel	Topical hands/ feet cryotherapy (N: 21)	Standard care (N: 21)	CIPN symptoms (EORTC QLQ-CIPN20)	6 months after chemotherapy	Per protocol analysis (39/46, 85 % patients completed the trial)	No significant differences between groups	2B
Beijers et al., 2020	Multicenter open-label RCT	N: 180 (M: 78, W: 102; age: 60.0 ± 9.7)	Colorectal, prostate, breast, ovary	Oxaliplatin, paclitaxel, docetaxel	Elasto-Gel Hypothermia gloves on both hands (N: 90)	Control condition not wearing gloves (N: 90)	CIPN symptoms (EORTC QLQ-CIPN20); QoL (EORTC QLQ-C30); tolerance to glove (NRS)	6 months after chemotherapy	ITT and per protocol analysis (73% patients completed the follow-up)	Reduction of tingling and cramps in finger/ hands, improvement of QoL, and physical functioning both to ITT and per-protocol analyses for the cryotherapy vs. control group when analysing single EORTC QLQ-CIPN20 and EORTC QLQ-C30 items but not the overall scores	2B
Kanbayashi et al., 2020	Prospective self controlled trial	N: 38 women (age: 57.6 ± 11)	Breast	Nab-paclitaxel	Frozen glove on one hand (60 min)	Two surgical gloves (compression) on	CTCAE v 4.0; PNQ; FACT-Taxane;	6 weeks after chemotherapy	Per protocol analysis (38/43, 88	No differences between group except	2C

Ref	Study design	Population	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
						the other hand (90 min)	fingertip temperature		% patients completed the trial)	fingertip temperature lower in the frozen vs. surgical glove hand	
	RCT		Breast	Paclitaxel				No	ITT analysis		2B
Shigematsu et al., 2020		N: 44 women (age: 66–77)			Hand/feet cryotherapy with frozen gloves/ socks (90 min; N: 22)	Control group (N: 22)	CIPN symptoms (FACT/GOG-Ntx; PNQ; CTCAE; FACT-Taxane); safety (localized skin symptoms; general symptoms of bodily chills; headache) and compliance to cryotherapy (appropriate positioning of frozen gloves/ socks)			Reduction of FACT-NTX scores, incidence of CTCAE grade > 2 CIPN, PNQ grade ≥ D, and FACT-T score for cryotherapy vs. control group; compliance: 68 %	
Electrical stimulation (Included, N = 24; completed the study, N = 24; sample size: N = 24)											
Tonezzer et al., 2017	RCT	N: 24 (M: 19, W: 5; age: 49.2 ± 12)	Breast, colorectal	Oxaliplatin, paclitaxel	Real TENS (7–65 Hz, daily for 45 days, distal limb regions; N: 11)	Sham TENS (N: 13)	Pain, numbness/ tingling, symptoms frequency, QoL (VAS); CTCAE; ECOG Performance Status scale;CINQ	No	ITT analysis	No significant 3B differences between active and sham TENS	2B

6MWT: six minutes walking test; ADL: activities of daily living; BBS: Berg Balance Scale; BFI: Brief Fatigue Inventory; BIA: bioelectrical impedance analysis; BPI: brief pain inventory; CEBM: Oxford Center for Evidence-Based Medicine [23]; CINQ: Chemotherapy Induced Neurotoxicity Questionnaire; CIPN: chemotherapy induced peripheral neuropathy; CMAP: compound motor action potentials; CPET: maximum cardiopulmonary exercise test; CRT: chair rising test; CTCAE: Common Terminology Criteria for Adverse Events; DASH: Disability of the Arm, Shoulder, and Hand; DN4: Douleur Neuropathique 4; EORTC QLQ-BR23: European Organization on Research and Treatment of Cancer breast cancer questionnaire; EORTC QLQ-CIPN20: European Organization for Research and Treatment of Cancer chemotherapy induced peripheral neuropathy questionnaire; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FAB: Fullerton Advanced Balance; FACT-GOG: Functional Assessment of Cancer Therapy/Gynaecology Oncology Group; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity questionnaire; FACT-Taxane: Functional Assessment of Cancer Therapy- Taxane; FEDA: Fragebogen Erlebter Defizite der Aufmerksamkeit; GGT-Reha: the German word

for balance test BGleichgewichtstest; h1RM: hypothetical one repetition maximum; HADS: Hamilton anxiety and depression scale; ITT: intention to treat; LOS: Limits of Stability Test; mCTSIB: Modified Clinical Test of Sensory Interaction on Balance; MFI-20: multidimensional fatigue inventory; MNA: Mini Nutritional Assessment; NCS: nerve conduction study; NCV: nerve conduction velocity; NPSI: Neuropathic Pain Symptom Inventory; NRS: numerical rating scale; NS: not specified; NtxS: neurotoxicity scale; PFS = Piper Fatigue Scale; PNQ: Patient Neurotoxicity Questionnaire; QoL: quality of life; QST: Quantitative sensory testing; RCT: randomized controlled trial; SGA: Subjective Global Assessment questionnaire; S-LANSS: Self-Leeds assessment of neuropathic symptoms and signs; SNAP: sensory nerve action potential; SPPB: short physical performance battery; STS: Sit to Stand Test; TENS: transcutaneous electrical nerve stimulation; TNS: Total Neuropathy Score; UICC: International Union Against Cancer; US: Unilateral Stance Test; VAS: visual analogue scale.

*marks studies that explored multiple treatments.

Table 4

Results of treatment studies for CIP

Ref	Study design	Population	CIPN severity at baseline	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
Exercise training (Included, N = 79; completed the study, N = 79; active intervention, N = 51; control group, N = 28; sample size: N = 79)												
Gui et al., 2021	Quasi-experimental study	N: 79 (M: 52, W: 27; age = 50.7 ± 7.7)	FACT/GOG-Ntx (active intervention: 17.1 ± 4.4; comparator: 16.9 ± 4.1)	Colorectal, gastric, pancreatic, liver	Oxaliplatin	Exercise rehabilitation program (comprehensive gymnastics + quickly walking training, 2 weeks)	Standard care (N: 28)	CIPN symptoms (FACT/GOG-Ntx); physical function (6-hole shirt, fifty step walking, coin test/total time); pain (BPI)	No	Probably ITT	Improvement of the FACT/ GOG-Ntx, functional tests and BPI scores for exercise rehabilitation program vs. standard care	2B
Balance and sensorimotor training (Included, N = 148; completed the study, N = 136; active intervention, N = 65; control group, N = 71; sample size: N = 22—45)												
Schwenk et al., 2016	Pilot singleblind RCT	N: 22 (M: 9, W: 13; age = 70.3 ± 8.7)	Vibration perception threshold >25 V	Lung, multiple myeloma, breast, colorectal, melanoma, bladder, prostate, pancreatic, chronic lymphoid leukemia	NS	Balance training protocol (2 session/ week, 45 min/ session over 4 weeks; N: 9/ 11 completed the study)	Standard care (N: 10/ 11 completed the study1)	Balance measures (ankle and hip sway); gait performance (speed, variability); fear of falling (FES-I)	No	Per protocol analysis (19/22, 86 % patients completed the trial)	Reduction of ankle and hip sway for balance training vs. control group	2B
Kneis et al., 2019	RCT	N: 41 (M: 11, W:30; median age: 62, range: 44–82)	NtxS (active intervention: mean 29, range 11—40; comparator: mean 31, range 16–39)	Breast, colorectal, gynecologic, gastrointestinal, lung, non-Hodgkin lymphoma, multiple myeloma	NS	Endurance and balance training (60 min, 2 session/ week, 12 weeks; N: 18/20 completed the study)	Endurance training (30 min, 2 session/ week, 12 weeks; N: 19/21 completed the study)	Balance measures (STeo, STec, MSeo, Mseo unstable); lower body muscle power (maximum power output); CIPN symptoms (EORTC QLQ-CIPN20, FACT/ GOG-Ntx); Rydel- Seiffer tuning fork; QoL (EORTC QLQ-C30); cardiorespiratory fitness (CPET)	No	Both per protocol and ITT analysis	Per-protocol-analysis (N = 37): improvement of balance measures and maximum power output, reduction of sensory symptoms and jump height for experimental than control group. No significant changes	2B

Ref	Study design	Population	CIPN severity at baseline	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
											(ITT analysis).	
Streckmann et al., 2019 *	RCT	N: 40 (CIPN: 30, healthy controls: 10; M:13, W:27; mean age: 57.8, range 47–74)	NS	Breast, ovary, colorectal, pancreatic, Hodgkin lymphoma, plasmocytoma, multiple myeloma, lung	Taxane, platinum, vinca alkaloid	Sensorimotor training (twice/ week, 6 weeks; N: 10) and whole body vibration (twice/ week, 6 weeks; N: 10)	Standard care (N: 10); healthy controls (N: 10)	CIPN standardized clinical battery; neuropathic symptoms (FACT/ GOG-Ntx); NCS measures (SNAP, CMAP amplitude); balance control (force plate); QoL (EORTC QLQ- C30); neuropathic pain (Pain DETECT)	No	Per protocol analysis (39/40, 98% patients completed the trial)	Reduction of FACT and CIPN clinical battery severity to sensorimotor training vs. other groups	2B
Dhawan et al., 2020 *	RCT	N: 45 (M: 7, W: 38; age: 51.5 ± 7.2)	Neuropathy symptoms experience scores (active intervention: 132.5 ± 30.3, comparator: 129.3 ± 40.1); neuropathy interference score (active intervention: 58.6 ± 14.2, comparator: 57.8 ± 9.9)	Ovary, cervix, lung	Paclitaxel and carboplatin	Home-based muscle strengthen and balance exercise (10 weeks, N: 19/22 completed the study)	Standard care (N: 22/ 23 completed the study)	Neuropathic pain (S-LANSS); QoL (EORTC QLQ-C30)	No	Per protocol analysis (41/45, 91 % patients completed the trial)	Significant improvement of neuropathic pain and QoL in active than control group	2B
Neurofeedback (Included, N = 71; completed both studies, N = 51; active intervention, N = 23; control group, N = 28; sample size: N = 71)												
Prinsloo et al., 2017	Pilot RCT	N: 71 (M: 9, W: 62; age = 62.5 ± 10.3)	NCI-CTC adverse event ≥ 3; CIPN-related pain NRS ≥ 4; duration ≥ 3 months	Breast, gastrointestinal, gynecologic	Platinum, taxane	Neurofeedback (20 sessions, 45 min/ session, twice/ week, 10 weeks; N: 30/35 completed the study)	Waiting list (N: 32/ 36 completed the study)	Pain severity and daily life impact (BPI); affective interference (BPI); pain characteristics (PQAS)	No	Per protocol analysis (62/71, 87 % patients completed the trial)	Reduction of BPI and PQAS to active vs. control group	2B
Prinsloo et al., 2018	RCT	N: 71 (M: 9, W: 62; age = 62.5 ± 10.3)	NCI-CTC adverse event ≥ 3; CIPN-related pain	Breast, gastrointestinal, gynecologic	Platinum, taxane	Neurofeedback (20 sessions, 45 min/ session, twice/ week, 10 weeks; N:	Waiting list (N: 28/ 36 completed the study)	Pain severity and daily life impact (BPI); pain characteristics	4 months	Per protocol analysis (51/71, 72 %	Reduction of BPI, PQAS, MDASI, improvement of SF-36 at	2B

Ref	Study design	Population	CIPN severity at baseline	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
			NRS ≥ 4; duration ≥ 3 months			23/35 completed the study)		(PQAS); cancer related symptoms (MDASI); QoL (SF-36); fatigue (BFI); sleep disturbances (PSQI)		patients completed the trial)	follow-up to active vs. control group	
Massage and related techniques (Included, N = 207; completed both studies, N = 171; active intervention, N = 86; control group, N = 85; sample size: N = 48—96)												
Park and Park, 2015	Quasi-experimental study	N:48 (M: 29, W: 19; age: 58.9 ± 10)	NCI-CTC adverse event 2–3	Colorectal, gastric	Platinum, taxane	Foot bathing (30 min session, 8 sessions, 2 weeks, every other day; N: 24)	Massage (30 min session, 8 sessions, 2 weeks, every other day; N: 24)	Foot skin temperature; Plasma calcium and magnesium; QoL (FACT-G, FACT/GOG-NTx)	No	Probably ITT	Foot skin temperature increased in the foot bathing and decreased in the massage group; QoL increased in the foot bathing and decreased in the massage group	2B
Kurt and Can, 2018	Pilot RCT	N: 96, of whom 60 (M: 32, W: 28; age = 58.1 ± 10.8) completed the study	Grade 2– 4 CIPN	Breast, gastrointestinal system	Platinum, taxane	Reflexology (20 min/ session, twice/ day, 6 weeks; N: 30/46 completed the study)	Standard care (N: 30/ 50 completed the study)	QoL (EORTC QLQ- CIPN20); pain (BPI)	No	Per protocol analysis (60/96, 63 % patients completed the trial)	No significant differences between groups	2B
Noh and Park, 2019	RCT	N: 63 women (age: 55.9 ± 9)	Individuals taking medication for CIPN control	Ovarian, cervical, endometrial	Platinum, taxane	Early intervention (aroma self-foot reflexology; 6 weeks; N: 32/33 completed the study)	Delayed intervention (N: 31/33 completed the study)	CIPN symptoms and interference with ADL; skin temperature; HADS	No	Per protocol analysis (63/66, 95 % patients completed the trial)	Lower CIPN symptoms, less interference with ADL, higher skin temperature level, lower HADS to early vs. delayed intervention	1B
Electrical stimulation (Included, N = 207; completed the study, N = 199; active intervention, N = 99; control group, N = 100; sample size: N = 35—72)												
Loprinzi et al., 2020b	Phase II RCT	N: 50 of whom 46 (M: 12, W:	Pain/tingling NRS ≥ 4, ECOG	NS	Paclitaxel, docetaxel, carboplatin,	Scrambler therapy (30 min/session over 2 weeks; N:	TENS (at home treatment, 30 min/ day over 14 days;	Pain/tingling/ numbness severity (NRS);	8 weeks	ITT analysis	Greater reduction of CIPN	2B

Ref	Study design	Population	CIPN severity at baseline	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
		34; median age: 61, range: 32–82) completed the study	performance ≥2		oxaliplatin, cisplatin, bortezomib	24/25 completed the study)	N: 22/25 completed the study)	changes in neuropathy, pain, QoL (EORTC QLQ-CIPN20, GIC)			severity to scrambler therapy vs. TENS	
Smith et al., 2020	Pilot phase II RCT	N: 35 (M: 9, W: 26; age: 59.31 ± 8.9)	Pain/tingling NRS ≥ 4, ECOG performance: 0–3	Colorectal, breast, myeloma	NS	Scrambler therapy (30 min/session on the dermatomes above painful areas, over 10 days; N: 17)	Sham (electrodes over L3-L5 nerve roots, N: 18)	Pain (BPI); QoL (EORTC QLQ-CIPN20)	28, 60, 90 days	ITT analysis	No significant difference between active and sham groups	2B
Son et al., 2020	RCT	N: 72 women (age: 50 ± 8.9)	Pain NRS ≥ 5, ECOG perormance: 0–2	Breast	NS	Low-frequency electrostimulation (wristband device, 14 days, twice/day, 120 min; N:36)	Sham wristband device (N: 36)	CIPN symptoms NRS; TNS; EORTC QLQ-CIPN20; FACT-B; IPIE- CIPN	2 weeks	ITT analysis	CIPN cold arthralgia symptom better in the active vs. sham group	1B
Chiang et al., 2021	Pilot RCT	N: 50, of whom 46 completed first phase and 22 the crossover phase (M: 5, W: 17; median age: 61)	Pain/tingling NRS ≥ 4, ECOG performance ≥3	NS	Paclitaxel, oxaliplatin	Scrambler therapy (30 min/session over 2 weeks; initial phase N: 22, crossover phase N: 10)	TENS (at home treatment, 30 min/ day over 2 weeks; initial, N: 24; crossover, N: 12)	Pain/tingling/ numbness severity (NRS); changes in neuropathy, pain, QoL (GIC)	8 weeks after initial/ crossover phases	ITT analysis	No significant difference between the two groups	2B
Other physical interventions (Included, N = 379; completed the study, N = 302; active intervention, N = 150; control group, N = 152; sample size: N = 31 —131)												
Clark et al., 2012	Pilot RCT	N: 36, of whom 26 (M: 3, W: 23; age: 59.0 ± 8.6) completed the study	NtxS (28.4 ± 7.7)	Ovarian, colon, breast, appendiceal, non-Hodgkin lymphoma, brain, peritoneal, Hodgkin lymphoma (stage I -IV)	Taxane, platinum, vinca alkaloid	Reiki (N: 9); yoga (N: 9); meditation (N: 9); 60 min/ session, 6 sessions in 6 weeks; 19 patients completed the study	Holistic education (60 min/session, 6 sessions in 6 weeks; N: 7/9 completed the study)	CIPN symptoms (FACT/GOG-Ntx); psychological distress (BSI-18); QoL (FACT/GOG-Ntx, MAAS)	No	Per protocol analysis (26/36, 72 % patients completed the trial)	No difference between active groups	2B
Lindblad et al., 2016	RCT	N: 67 (M: 33, W: 34; age = 64.0 ± 10.7)	Chronic CIPN (referring physician diagnosis)	Uterine, pancreas, cervix, gastric, lymphoma, colorectal, ovarian, breast, basalioma, small-bowel	Oxaliplatin, cisplatin, taxane, vincristine, vinblastine, capecitabine	Interferential therapy and high-power longwave diathermy (12-weeks, once/week, 6 min/session; N: 24/ 34 completed the study)	Low power longwave diathermy (12-weeks, once/week, 6 min/session; N: 26/ 33 completed the study)	Pain (NRS); pain-drawing sketch; balance (DHI, Tightened Romberg test, one-legged stance test)	25 weeks	Per protocol analysis (50/67, 75 % patients completed the trial)	Reduction of pain intensity for control group at the end of treatment; increas in onelegged	2B

Ref	Study design	Population	CIPN severity at baseline	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
											stance test and reduction of tightened Romberg for experimental group at follow-up; no signficant difference between groups	
Argenta et al., 2017 *	Cross-over RCT	N: 70 women (age: < 50 - > 80)	NS	Gynecologic (ovarian, uterine, cervical), breast, hematologic, colorectal	Platinum, taxane	Photobiomodulation (3 session/week, 1—12 min/session, 6 weeks; 6.75–12 W; 20 KHz pulsed waveform or 800–970 nm continous waveform; N: 30)	Sham photobiomodulation (N: 40, of whom 38 crossed over and received photobiomodulation and physiotherapy with manual soft tissue mobilization, 15 min/session)	Neuropathy (mTNS)	16 weeks	ITT analysis	Reduction of mTNS up at follow-up to both active treatments vs. sham treatment; regression of benefit to active treatments at 16 weeks; no significant difference between active treatments	1B
Ricci et al., 2017	RCT	N: 44 (M:13, W: 31; median age: 58, range 28–73)	Grade 1– 4 CIPN	Lymphoma, breast, ovarian, colorectal	Platinum, taxane, vinca alkaloids	Magnetic field therapy (twice/day, 4–12 Hz, 420 m T, 5 min/ each extremity; N: 17/21 completed the study)	Sham magnetic field therapy (twice/ day, 5 min/each extremity; N: 14/23 completed the study)	NCS measures (NCV); patient subjective perceived neurotoxicity (CTCAE); neuropathic pain (PainDETECT)	3 months	Per protocol analysis (31/44, 70% patients	No significant difference between groups	1B
Schonsteiner et al., 2017 *	Pilot RCT	N: 131 (M: 63, W: 68; age: 54.4 ± 9.4)	NCI-CTC adverse event 2–3	Multiple myeloma, lymphoma, leukemia, breast, colorectal, lung, gastric, other	NS	Whole body vibration and an integrated program (massage, passive mobilization, physical exercise; 15 training sessions, biweekly basis; N: 44/66 completed the study)	Integrated program only (N: 50/65 completed the study)	QoL (EORTC QLQ-C30, v 3.0); lower limb tendon reflexes; Rydel-Seiffer tuning fork (C64); physical fitness and coordination (CRT); QST	1 month	completed the trial) Per protocol analysis (94/131, 72% patients completed the trial)	No significant difference between groups	2B

Ref	Study design	Population	CIPN severity at baseline	Cancer type(s)	Chemotherapy agent	Active intervention	Comparator	Primary/ secondary Outcomes	Follow-up	Type of analysis	Results	Level of evidence (CEBM)
Al Onazi et al., 2021 *	Pilot RCT	N: 31 (M: 10, W: 21; mean age: 60.1, range: 39–82)	NCI-CTC adverse event: 1— 3	Colorectal	Oxaliplatin, capecitabine	Low-intensity (0.7 to 0.8 w/cm2) ultrasound (3 MHz, 20 min/session, 10 sessions in 2 weeks) and standard care (home hand/feet exercise, balance program; one session/day, 6 weeks; N: 16)	Standard care (home hand/feet exercise, balance program; one session/day, 6 weeks; N: 15)	Pain and sensory disturbance (FACT-GOG-Ntx); QoL (EORTC QLQ-CIPN20); Semmes-Weinstein monofilament; hot/cold discrimination; vibration detection (128-Hz tuning fork); deep tendon reflexes; balance (modified Clinical Test of Sensory Interaction on Balance, single leg stance test)	6 weeks	ITT analysis	Improved upper extremity vibration and reduction of FACT-GOG-Ntx at 3 weeks but not at 6 weeks to active vs. control treatment	2B

ADL: activities of daily living; BFI: Brief Fatigue Inventory; BPI: brief pain inventory; BSI-18: Brief Symptom Inventory 18; CEBM: Oxford Center for Evidence-Based Medicine [23]; CIPN: chemotherapy induced peripheral neuropathy; CMAP: compound motor action potentials; CPET: maximum cardiopulmonary exercise test; CRT: chair rising test; CTCAE: Common Terminology Criteria for Adverse Events; DHI: Dizziness Handicap Inventory; DN4: Douleur Neuropathique 4; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-BR23: European Organization on Research and Treatment of Cancer breast cancer questionnaire; EORTC QLQ-CIPN20: European Organization for Research and Treatment of Cancer chemotherapy induced peripheral neuropathy questionnaire; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; FACT-B: Functional Assessment of Cancer Therapy Breast; FACT-G: Functional Assessment of Cancer Therapy General; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group-Neurotoxicity; FES-I: falls efficacy scale international; GIC: Global Impression of Change questionnaire; HADS: Hamilton anxiety and depression scale; IPIE-CIPN: Instrument on Pattern Identification and Evaluation for CIPN; ITT: intention to treat; MAAS = Mindful Attention Awareness Scale; MDASI: MD Anderson Symptom Inventory; MSeo: monopedal stance; mTNS: modified total neuropathy score; NCI-CTC: National Cancer Institute Common Toxicity Criteria; NCS: nerve conduction study; NCV: nerve conduction velocity; NRS: numerical rating scale; NS: not specified; NtxS: neurotoxicity scale; PQAS: pain quality assessment; PSQI: Pittsburgh Sleep Quality Index; QoL: quality of life; QST: Quantitative sensory testing; RCT: randomized controlled trial; SF-36: Short Form Health Survey; S-LANSS: Self-Leeds assessment of neuropathic symptoms and signs; SNAP: sensory nerve action potential; STec: semi-tandem stance (eyes closed); STeo: semi-tandem stance (eyes open); TENS: transcutaneous electrical nerve stimulation; TNS: Total Neuropathy Score

* marks studies that explored multiple treatments.

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Table 5

Recommendations on rehabilitation, exercise, and physical therapies for CIPN prevention and treatment.

Recommendation	Level of evidence (OECBM)
Exercise, endurance, and strength training	
CIPN prevention. Moderate quality evidence suggests that exercise during chemotherapy may improve sensory symptoms, prevent strength loss, improve balance, and stabilize the functional capacity of patients. Exercise and multimodal physical training may reduce falls and fall-related injury	B
CIPN treatment. Preliminary data suggest that exercise may improve CIPN symptoms, functional tests, and pain	C
Balance and sensorimotor training	
CIPN prevention. Low-to-moderate quality evidence suggests beneficial effects on balance, pain, muscle strength, and fitness	B
CIPN treatment. Low-to-moderate evidence suggests improvement in balance function, postural control, quality of life level, and reduction in symptom severity	B
Neurofeedback	
CIPN prevention. No evidence	Undetermined
CIPN treatment. Preliminary data suggest that neurofeedback may improve pain, quality of life and fatigue	C
Massage and related techniques	
CIPN prevention. Inconclusive evidence to suggest that massage and related techiques may prevent CIPN symptoms	D
CIPN treatment. Inconclusive evidence to suggest that massage and related techiques are effective on pain, daily function, or quality of life	D
Cryotherapy and compression therapy	
CIPN prevention. Inconclusive evidence to suggest that cryotherapy and compression therapy may prevent CIPN symptoms	D
CIPN treatment. No evidence	Undetermined
Electrical stimulation	
CIPN prevention. Very preliminary data suggest no effect on CIPN prevention	D
CIPN treatment. Very preliminary data suggest some effect on pain	D
Other physical therapies	
CIPN Prevention. No evidence	Undetermined
CIPN treatment. Inconclusive evidence to suggest that other physical therapies are effective on pain, daily function, or quality of life	D

CIPN: chemotherapy-induced peripheral neuropathy. CEBM: Oxford Center for Evidence-Based Medicine grades of recommendation (A: consistent level 1 studies; B: consistent level 2 or 3 studies or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level) (Oxford Centre for Evidence-Based Medicine Levels of Evidence Working Group (OECBM, 2009).