Physical therapy for deficits associated with chemotherapy-induced peripheral neuropathy in children with cancer: a systematic review

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent and debilitating side effect seen in children undergoing chemotherapy. Objective: To synthesize the evidence on physiotherapy for CIPN symptoms and deficits in children with cancer. Methods: A systematic review was conducted with the following PICOS approach: children with cancer, physiotherapy, control group or standard care, and randomized controlled trials and controlled clinical trials comprising range of motion, muscle strength, motor function, balance, gait, functional mobility, foot posture, pain, and adverse events outcomes. Searches were conducted in five electronic databases, reference lists, grey literature, and clinical trial websites in May 2023. Results: Nine full-text studies met the inclusion criteria. Although benefits were seen for some outcomes related to physical function, evidence is not at a stage to provide recommendations for clinical practice. Conclusion: Research is needed that includes CIPN-specific outcome measures to better inform the incidence, natural progression, and the benefits of physiotherapy interventions.

Physical therapy for deficits associated with chemotherapy-induced peripheral neuropathy in children with cancer: a systematic review

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Abbreviations table

Abbreviations	Full term
CIPN	Chemotherapy-induced Peripheral Neuropathy

Abbreviations	Full term
ALL	Acute Lymphoblastic Leukemia
PT	Physical Therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
CCT	Controlled Clinical Trial
EORTC	European Organization for Research and Treatment of Cancer
QLQ-CIPN20	Quality of Life Questionnaire-CIPN twenty-item scale
ped-mTNS	Pediatric Modified Total Peripheral Neuropathy Score
TNS-PV	Total Neuropathy Score-Pediatric Vincristine
TNS	Total Neuropathy Score
ROM	Range of Motion
BOT-2	Bruininks Osteretsky Test of Motor Proficiency Second Edition
PDMS-2	Peabody Developmental Motor Scales
6-MWT	6-minute Walk Test
2-MWT	2-minute Walk Test
9-MWT	9-minute Walk Test
TUG	Timed Up and Go Test
TUDS	Timed Up and Down Stairs
FP1-6	Foot Posture Index
VAS	Visual Analog Scale
ROB 2	Cochrane risk-of-bias tool for randomized trials
BOTSF-2	Bruininks-Oseretsky Test of Motor Proficiency Short Form
GMFM-ALL	Gross Motor Function - Measure-Acute Lymphoblastic Leukemia Scale
BSID-II	Dutch Bayley Scales of Infant Development II
Movement-ABC	The Movement Assessment Battery for Children
MRC	Medical Research Council
PBS	Pediatric Balance Scale

ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent and debilitating side effect seen in children undergoing chemotherapy. Objective: To synthesize the evidence on physiotherapy for CIPN symptoms and deficits in children with cancer. Methods: A systematic review was conducted with the following PICOS approach: children with cancer, physiotherapy, control group or standard care, and randomized controlled trials and controlled clinical trials comprising range of motion, muscle strength, motor function, balance, gait, functional mobility, foot posture, pain, and adverse events outcomes. Searches were conducted in five electronic databases, reference lists, grey literature, and clinical trial websites in May 2023. Results: Nine full-text studies met the inclusion criteria. Although benefits were seen for some outcomes related to physical function, evidence is not at a stage to provide recommendations for clinical practice. Conclusion: Research is needed that includes CIPN-specific outcome measures to better inform the incidence, natural progression, and the benefits of physiotherapy interventions.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, often long lasting, and severe side effect in childhood cancer, resulting from the administration of neurotoxic chemotherapy agents such as vinca alkaloids (*e.g.,* vincristine) and platinum compounds (*e.g.,* cisplatin).[1-3]

The pathogenesis of pediatric CIPN is not well understood, possibly due to most mechanistic evidence coming from animal models and adult patients.[4] Peripheral neuropathies may result from the damage caused by neurotoxic agents to sensory axons, usually in the dorsal root ganglia, of the primary sensory neurons.[5-7]

The damage from neurotoxic agents causes degeneration and death of axons, myelin sheaths, or cell bodies,[3,8] which may lead to long-term functional abnormalities and structural lesions in both peripheral and central nervous systems.[8]

Pathophysiological mechanisms of CIPN differ between children and adults given the differences in the myelination of peripheral nerves, composition of the immune system, and central nervous system neuroplasticity.[9-11] Consequently, the clinical manifestations are different in children, with vincristine-induced motor neuropathies more commonly seen in children, presenting as muscle weakness, foot drop, ataxia, and impaired gait.[12,13]

CIPN is usually presented in a bilaterally symmetrical distribution, manifesting first in the lower extremities in a stocking-pattern, followed by the upper extremities in a glove-pattern of distribution.[3,8,14,15] CIPN primarily affects small-diameter sensory nerve fibers, causing symptoms such as pain or dysesthesia.[15] Impairments in large-diameter sensory fibers result in a loss of proprioception, decreased vibratory sense, decreased deep tendon reflexes, numbness, and loss of fine touch.[3,8,15,16] Secondary deficits include motor impairments such as distal weakness progressing to foot drop and atrophy.[3,14-17] These deficits lead to balance and coordination impairments, muscle contractures, skeletal malalignment, and abnormal gait patterns (*e.g.,* slowed velocity).[3,8,15,16,18,19]

CIPN symptoms and deficits can appear early in therapy and persist at least 12 months post-therapy.[20] Lavoie Smith et al.,[21] found that 78% of children with acute lymphoblastic leukemia (ALL) presented with CIPN during the first year of treatment, with a prevalence peak in the first 2 to 4 months of cancer treatment. Two cross-sectional studies have shown that 30 to 40% of children with ALL, 2 to 3 years post-treatment, experience peripheral nerve deficits,[22,23] and 12 to 40% of long-term survivors receiving neurotoxic chemotherapy agents experience neurological impairments 10 years following completion of cancer treatment.[24,25]

Research has documented that patients refer to CIPN as one of the most distressing symptoms experienced.[3]Associated sequelae may lead to limitations in daily activities (*e.g.,* running), as well as restrictions in participation (e.g., sports); all of which can negatively affect the quality of life of children and adolescents.[18]

Physical therapy (PT) for CIPN plays an important role by helping to prevent deformities, promote patient safety, maintain or restore function, and maximize independence in daily life activities.[26,27]Although there is a paucity of high-quality studies evaluating CIPN as a clinical entity in the pediatrics population, there are studies that have been conducted examining physiotherapy interventions for symptoms and deficits resulting from CIPN[28-31]. Preliminary research evidence supports the benefits of rehabilitation interventions to address side effects such as decreased ankle range of motion (ROM) and foot drop—side effects resulting from CIPN.[32]Therefore, the aim of this systematic review is to synthesize the research evidence on PT interventions for symptoms and deficits associated with CIPN in children with cancer.

2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The review protocol was registered in PROSPERO (CRD42023429838).

2.1. Search strategy and selection criteria

Search strategies were developed with the assistance of a medical librarian at the University of Alberta, and the filter by Glanville et al.,[33] was used to find clinical trials. Searches were executed in five electronic databases: Medline, Embase, CINAHL, CENTRAL, and Scopus (Supplemental Document S1). Additional searches were also conducted for reference lists of relevant articles, grey literature, and clinical trial websites. Literature published up to May 2023 was reviewed for inclusion.

Titles and abstracts were reviewed for eligibility by one author (PO) and were included if met the following PICOS approach criteria: population, children (any age) with any type of cancer; intervention, PT interventions for CIPN or its associated deficits, including therapeutic exercise, manual therapy, electrophysical agents, gait and balance retraining, joint mobilization, proprioception, coordination, or orthoses (i.e., splints,

ankle-foot orthoses, ankle straps); comparison intervention, standard care, placebo, no PT, or comparison treatment; outcomes, CIPN symptoms, ROM, muscle strength, motor function, balance, gait, functional mobility, foot posture, pain, and adverse events; study design, randomized controlled trial (RCT) or controlled clinical trial (CCT).

Studies were excluded if the intervention comprised interventions that aimed at increasing physical activity levels or fitness, and not at treating a CIPN deficit, symptom, or impairment.

Retrieved articles were imported into COVIDENCE.[34]Titles and abstracts were screened for full-text review by one author (PO). Full articles were reviewed by two authors (PO, MAO). Disagreements on inclusion were resolved by discussion and consensus, or if necessary, a third reviewer (MM) was consulted to reach consensus.

2.2. Data collection

Two review authors (PO, MAO) extracted the characteristics for each study using a data extraction form, and a third reviewer (MM) reviewed the data extracted. Extracted data included information on the trial design, sample size, characteristics of participants, objectives of the study, type of intervention(s) for intervention and comparison groups, duration of intervention, outcomes assessed, study results.

The primary outcome of interest of this review is CIPN symptoms measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-CIPN twenty-item scale (QLQ-CIPN20), Pediatric Modified Total Peripheral Neuropathy Score (ped-mTNS), Total Neuropathy Score-Pediatric Vincristine (TNS-PV), Total Neuropathy Score (TNS), sensory testing (monofilament testing, nerve conduction testing), or another valid instrument.

Secondary outcomes of interest included *ROM* , measured by goniometry; *muscle strength* , measured by manual muscle testing, dynamometry, or another valid instrument; *motor function* , assessed by the Bruininks Osteretsky Test of Motor Proficiency Second Edition (BOT-2), Peabody Developmental Motor Scales (PDMS-2), or another valid instrument; *balance* , assessed using the Single Leg Stance, Flamingo Balance Test, The Berg Balance Test, or another valid instrument; *gait* , assessed by observational or computerized analysis, or another valid instrument; *functional mobility* , assessed by the 6-minute walk test (6-MWT), 2-minute walk test (2-MWT), 9-minute walk test (9-MWT), Timed Up and Go test (TUG), Timed Up and Down Stairs (TUDS), or other another valid instrument; *foot posture* , assessed by the Foot Posture Index (FP1-6) or another valid instrument; *pain* , measured by the Visual Analog Scale (VAS) or another valid instrument; and *adverse events* , resulting from the PT intervention including falls, fractures, soft tissue injuries, and worsening of symptoms (*e.g.,* increased pain) that require study withdrawal.

2.3. Data analysis

We did not pool the data from the included trials due to heterogeneity among study populations, as well as chosen outcomes, interventions and comparisons. Therefore, as per protocol, we conducted a descriptive analysis of the outcomes.

2.4. Quality appraisal

The methodological quality of the RCTs and CCTs was assessed using the Cochrane risk-of-bias tool for randomized trials (ROB 2) assessment to ensure consistency in reporting as the clinical trials followed the same RCT methodology. Two review authors (PO, MAO) independently assessed the risk of bias in the studies using the revised ROB 2 tool,[35] rating each risk-of-bias item as 'low risk of bias', 'some concerns', or 'high risk of bias'. Disagreements were resolved by discussion, or if necessary, a third reviewer (MM) was consulted to reach consensus. The third author (MM) also reviewed the assessments.

3. Results

3.1. Description of studies 3.1.1. Search results

The searches of the five electronic databases, reference lists of relevant articles , grey literature, and clinical trial websites retrieved a total of 4451 references (Fig. 1). Titles and abstracts screening resulted in 41 full-text studies assessed for eligibility. Thirty-two studies did not meet the eligibility criteria, resulting in nine studies included in the review. Ongoing studies were reported in the 'Ongoing studies' section (Supplemental Document S2).

3.1.2. Study Designs

Of the nine studies included in the review, six studies were RCTs,[32,36-40] one was a pilot RCT with preliminary results only,[41] one was a CCT,[42] and one was a pilot CCT.[43] The secondary analysis[44] of an RCT [42] was included in the review (Table 1).

3.1.3. Participants

A total of 439 participants were included in the studies. Five studies included children diagnosed with ALL,[32,36-38,40] two studies included children with any type of cancer,[39,45] and two studies included children scheduled for/ receiving hematopoietic stem cell transplant.[42,43] Ages varied across the studies, from 4 to 19 years, and sample sizes ranged from 7 participants to 107 participants.

3.1.4. Outcomes

None of the studies included a CIPN-specific outcome assessment; however, all studies included at least one outcome that assessed an impairment impacted by CIPN. Four studies assessed endurance/ functional capacity using the 6-MWT[36,42] and 9-MWT[32,38]; four studies assessed motor proficiency using the Bruininks-Oseretsky Test of Motor Proficiency Short Form (BOTSF-2)[36,39], Gross Motor Function - Measure-Acute Lymphoblastic Leukemia Scale (GMFM-ALL)[43], Dutch Bayley Scales of Infant Development II (BSID-II)[37], and The Movement Assessment Battery for Children (Movement-ABC)[37]; four studies assessed functional mobility using the TUDS[32,38,42], TUG[32,42,43], and the time needed to stand up from bed rest exam[42]; three studies assessed active ankle ROM using a goniometer[32,36,38]; three studies assessed hand-grip strength using a dynamometer[36,38,42]; three studies assessed knee extension strength using a dynamometer[36,38] and the Medical Research Council (MRC) grading system[43]; three studies assessed ankle dorsiflexion strength using a dynamometer[36,38] and the MRC grading system[43]; two studies assessed lower body strength using a dynamometer[32] and the 30-sec chair-stand test[42]; two studies assessed passive ankle ROM using a goniometer[37,43]; two studies assessed pain intensity using the VAS[41] and the Wong-Baker FACES Pain Rating Scale[44]; one study assessed pain threshold using an algometer[41]; and one study assessed balance using the Pediatric balance scale (PBS)[40]. Only three studies provided data on adverse events and these studies indicated that no adverse events occurred as a result of the interventions.[38,42,43]

3.1.5. Interventions

Most of the studies (n= 6) included an exercise program within their intervention, comprising strength, ROM, and aerobic/ endurance exercises.[32,36-38,42,43] Some studies added additional components such as behaviour change intervention and exercises for gross motor skills,[36] education on motor impairments,[37] manual stretching and functional exercises,[38] rehabilitation counseling indications,[43] and relaxation exercises.[42] Of the nine studies included in the review, only one evaluated a PT intervention for CIPN-related pain,[41] and eight evaluated the effect of the intervention on deficits resulting from CIPN.[32,36-40,42,43] The PT interventions evaluated across the studies were heterogeneous, comprising hospital-based programs,[40,41,43] and a combination of in-hospital and home-based programs.[32,36-39,42] One study included graded motor imagery and neural mobilization interventions,[41] one included task-oriented rehabilitation interventions including functional activities for fine and gross motor skills,[39] and one included gait training and balance training interventions.[40]

Duration of interventions ranged from 4 weeks to 2.5 years, with a frequency of daily sessions to monthly sessions. Frequency of sessions varied across the studies as some included more than one intervention with different frequency of sessions. Six studies evaluated interventions with a frequency ranging from 2 to 5 days

per week,[32,36,38,40,41,43] and three studies comprised interventions that were delivered and/or recommended on a daily basis.[37,39,42] Two studies evaluated long-term interventions lasting 2 [37] and 2.5 years.[36]

Results suggest that studies that comprised shorter supervised and tailored PT interventions showed better results compared to those examining long-term unsupervised interventions. Marchese et al.,[38] evaluated a 4-month combined in-hospital and home-based PT intervention comprising functional exercises compared to no PT exercises and advice. Results showed statistically significant improvements in ankle dorsiflexion ROM ($p<0.01$) and knee extension strength ($p<0.01$). Sahin et al.,[39]examined the effects of a 4-week in-hospital home-based task-oriented rehabilitation program including functional gross and fine motor activities compared to a home-based program. Results showed moderate effect sizes in gross and fine motor skills in the intervention group and no effect in the control group. Zakaria et al.,[40]investigated the effect of a 3-month in-hospital PT program combining gait and balance training, compared to gait training alone. Results showed significant improvement in balance scores in the intervention group ($p<0.001$). Tanir et al.,[32] evaluated a 3-month combined supervised in-hospital and home-based PT intervention comprising strengthening, ROM, and aerobic exercises compared to no exercise recommendations. Results showed statistically significant improvements in functional capacity and leg strength ($p=0.001$). Yildiz et al.,[42] investigated the effectiveness of a supervised exercise program during hospitalization combined with a self-administered home-based program 1 month after discharge, compared to recommendations to stay active during hospitalization. Results showed statistically significant group differences were found favouring the intervention group for functional capacity ($p=0.021$), lower body strength ($p=0.012$), and functional mobility ($p<0.001$) outcomes. Rossi et al.,[43] evaluated the preliminary effectiveness of a hospital-based rehabilitation program in addition to rehabilitation counseling indications in maintaining motor performance. Results showed that participants maintained their motor function and ankle ROM. Casanova-Garcia et al.,[41] investigated the effect of a 4-week graded motor imagery and neural mobilization intervention on neuropathic pain. Preliminary results ($n= 7$) showed a trend of improvement in pain intensity.

While studies that evaluated shorter and tailored PT interventions showed good adherence,[32,38,39,42] studies that evaluated long-term interventions starting from diagnosis and finalizing upon cancer treatment completion, however, showed low adherence to the interventions. Hartman et al.,[37] investigated the effect of a 2-year exercise program comprising education on motor deficits resulting from chemotherapy in addition to a PT program to maintain function and mobility. Results showed low adherence to the intervention, with no change in outcomes between groups. The exercise program was found to be not more beneficial than standard of care. Cox et al.,[36] evaluated the effects of a 2.5-year combined in-hospital and home-based motivation-focused exercise program. Results showed low adherence to the intervention with no improvements in outcomes when compared to usual care.

3.1.6. Risk of bias assessments

All studies were classified as high-risk of bias.[35]All studies had at least one category scored as 'high-risk', with the most common bias resulting from deviations from intended interventions, which comprises blinding of participants and investigators to the intervention. Unfortunately, due to the nature of PT interventions, this bias is not possible to mitigate in most cases.

3.1.7. Ongoing studies

A total of five ongoing clinical trials ($n= 3$) and registered protocols ($n= 2$) were retrieved from the search. PT interventions being evaluated comprise sensorimotor training,[46,47] structured active play activities for gross motor function,[48] foot orthotics and splints,[49] and goal directed exercise therapy.[50] Three out of the five ongoing studies include CIPN symptoms as an outcome measured using the Ped-mTNS score[46,47,50] (Supplemental Document S2).

4. Discussion

This systematic review identified nine relevant studies examining the effects of therapeutic interventions for CIPN-associated deficits in children with cancer. The primary finding of this review is that none of the studies

assessed CIPN as a clinical entity, despite the focus on interventions that were tailored to address associated impairments. Our results are similar to recent reviews evaluating the effects of exercise for CIPN symptoms in that, to date, no high-quality studies have been published evaluating exercise or therapeutic interventions specific to CIPN symptoms nor including a CIPN-specific assessment in children with cancer.[29-31] Streckmann et al.,[30]attributes the paucity of research in this area to the under-reported statistics on its incidence and prevalence, and the limited evidence-based knowledge on assessment and treatment options in the pediatric population.[2,8]

CIPN is commonly seen in children receiving neurotoxic chemotherapy drugs, with prevalence rates reported in up to 100% of pediatric cancer patients,[2] lasting years following completion of cancer therapy.[22-25,51] A standardized CIPN assessment should be included as part of the routine PT assessment to allow an early detection and management of the condition,[52]even in cases where the frequency of vincristine doses has been reduced.

Reliable and validated pediatric-specific CIPN tools exist that can be used clinically. The Pediatric Modified Total Peripheral Neuropathy Score (ped-mTNS) is one of the most commonly reported tools used to assess CIPN in children as it comprises a comprehensive set of questions on sensory, motor, and autonomic functions, as well as physical tests comprising light touch, pin and vibration sensation, distal muscle strength, and deep tendon reflexes.[53] This tool requires a handheld Biothesiometer to measure vibratory thresholds, and this type of equipment may not be widely accessible. Incorporating a simple CIPN questionnaire within the routine PT assessment has shown value for early identification of CIPN symptoms in situations where resources are limited. Wang et al.,[54] conducted a survey including four questions on the severity of CIPN symptoms for children and their caregivers, and reviewed health records to explore the number of referrals to PT and utilization of the service. Results showed that 67.6% reported CIPN symptoms, with 16.7% scoring 4 or more, which is indicative of clinically severe CIPN. Despite concerns were reported on limitations in functional activities, only 55.1% of children were referred to PT.

Our review revealed that short-term, supervised, tailored therapeutic interventions showed positive benefits on functional outcomes affected by CIPN such as ankle dorsiflexion ROM, motor performance, lower extremity strength, functional mobility, functional capacity, and balance. Smaller studies also have shown benefits of PT interventions such as prescription of orthoses for deficits resulting from CIPN. Tanner et al.,[55] examined the feasibility of an ankle foot orthosis in children with non-central cancers experiencing peripheral muscle weakness and results showed positive trends in step length (p=0.028), dorsiflexion strength (p=0.046), and ankle dorsiflexion ROM (p= 0.027). Tanner et al.,[56]conducted a longitudinal, descriptive study to evaluate the feasibility of a proactive PT program 'Stoplight', targeting the main impairments resulting from ALL chemotherapy treatment in children. The intervention utilizes a prospective surveillance model to facilitate routine screening of CIPN and functional deficits in children receiving neurotoxic agents. The 'Stoplight' program offers education and preventive care interventions early after diagnosis, as well as tailored rehabilitation sessions for children demonstrating significant CIPN deficits. Thereafter, Tanner et al.,[57] conducted a quasi-experimental, between-subject study to investigate the sustained benefits of the 'Stoplight' program on body function and activity limitations in survivors of ALL who completed the program and compared them with an historical control group of children. Results showed benefit from the program for motor performance and physical activity levels 1.5 years after cancer treatment completion.

Findings from this review suggest that interventions that were tailored to the child's deficits and comprised functional activities resulted in positive benefits for some physical outcomes usually impaired by CIPN, in addition to good adherence to the interventions. These results are consistent with current research recommendations that support tailoring rehabilitation programs for CIPN impairments,[26] with a focus on maintaining function and independence in daily activities.[26] PT programs may focus on strengthening exercises to maintain and optimize muscle strength, stretching to preserve muscle length and minimize the risk of ROM loss, desensitization techniques to promote sensory processing and decrease pain, balance and gait retraining to optimize mobility, and bracing to support the affected extremities and maintain ROM.[26,58]

Although this review did not identify high quality research studies that included CIPN as an outcome, five

ongoing studies were identified, with some comprising play-based sensorimotor interventions for children with central nervous system cancers and ALL. Sensorimotor interventions have shown to be beneficial for adults with CIPN; however; it is still unknown if the evidence-based recommendations in adults can be transferred to the pediatric population.[30]Nonetheless, smaller scale, uncontrolled studies have examined the effects of novel therapeutic approaches such as whole body vibration for children during [59] and after receiving chemotherapy.[60]

Results from this systematic review indicate that research evidence on PT interventions for CIPN and its associated deficits in childhood cancer survivors is limited. Preliminary research shows positive benefits for some physical function outcomes affected by CIPN, but given the heterogeneity across interventions it is not possible to provide clear recommendations. Current ongoing studies exploring CIPN-specific interventions may provide needed insights to advance the field.

This systematic review presented some limitations. First, we only included studies that have been published. Therefore, our results may not reflect all the studies that have been conducted but are unpublished. Second, only one review author conducted the initial title and abstract screening; consequently, it is possible that we may have missed some relevant studies. Third, given the heterogeneity across studies, we were unable to pool the results to provide recommendations for clinical practice.

5. Conclusions

Preliminary research evidence demonstrates that therapeutic interventions may have the potential to improve ankle dorsiflexion ROM, motor performance, lower extremity strength, functional mobility, functional capacity, and balance outcomes–which are commonly associated with CIPN. Researchers should consider including a CIPN-specific tool to better inform the incidence, natural progression, and the benefits of PT interventions.

Conflict of Interest

The authors declare no conflict of interest.

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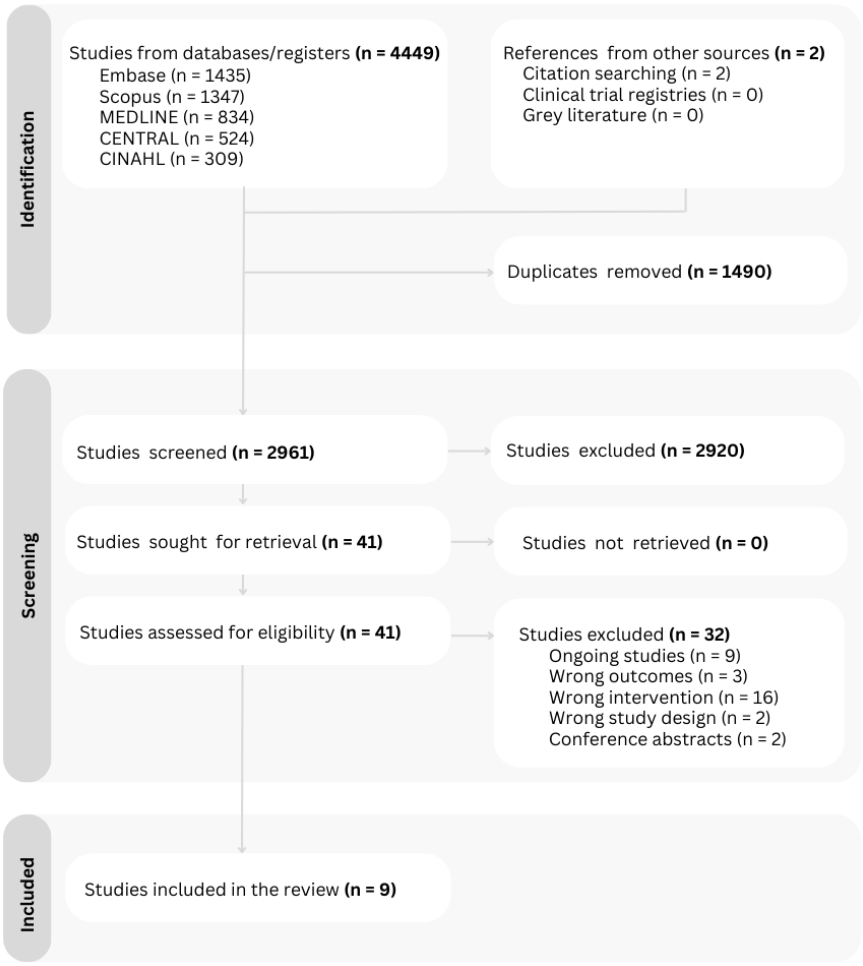

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