Review Article

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Effectiveness of Non-Pharmacological Interventions for Spasticity Management in Multiple Sclerosis: A Systematic Review

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This systematic review aims to determine the effectiveness of non-pharmacological interventions for the management of spasticity in people with multiple sclerosis (pwMS). A comprehensive literature search in health science databases (MEDLINE, Embase, CENTRAL, CINHAL) was performed to identify randomized controlled trials (RCTs) (up to April 2024). Manual searching in journals and screening of the reference lists of identified studies were conducted. Two authors independently selected the studies, assessed the methodological quality, and summarized the evidence. A meta-analysis was not feasible due to the methodological, clinical, and statistical diversity of the included studies. Overall, 32 RCTs (n=1,481 participants) investigated various types of non-pharmacological interventions including: physical activity, transcranial magnetic stimulation (intermittent theta burst stimulation [iTBS], repetitive transcranial magnetic stimulation [rTMS]), electromagnetic therapy, transcutaneous electrical nerve stimulation, vibration therapy, shock wave therapy, self-management educational programs, and acupuncture. All studies scored 'low' on the methodological quality assessment, implying a high risk of bias. The findings suggest 'moderate to low certainty' evidence for physical activity programs used in isolation or combination with other interventions (pharmacological or non-pharmacological), and for iTBS/rTMS with or without adjuvant exercise therapy in improving spasticity in adults with MS. There is 'very low certainty' evidence supporting the use of other modalities for treating spasticity in this population. Despite a wide range of non-pharmacological interventions used for the management of spasticity in pwMS, there is a lack of conclusive evidence for many. More robust trials with larger sample sizes and longer-term follow-ups are needed to build evidence for these interventions.

Keywords: Multiple sclerosis, Muscle spasticity, Systematic review, Rehabilitation

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disorder marked by patchy inflammation, gliosis, and demyelination within the central nervous system. The prevalence of MS is increasing, with an estimated 2.8 million people worldwide, or approximately 35.9 per 100,000 population, with an incidence rate of 2.1 per 100,000 persons per year [1]. MS manifests in various forms, with the majority (80%) classified as relapsing-remitting MS (RRMS), marked by episodes of exacerbation and remission that may transition to secondary progressive MS (SPMS), characterized by progressive disability between attacks. Other forms include primary progressive MS (PPMS, 15%), where disability progresses from onset, and progressive relapsing MS (PRMS, 5%), which involves gradual worsening followed by acute attacks. The median survival time from diagnosis of people with MS (pwMS) is estimated to be approximately 40 years, which is increasing due to advancements in medical management [2]. This longevity presents challenges such as progressive physical disability, psychosocial adjustment, and social reintegration, impacting not only the pwMS but also their caregivers, clinicians, and the healthcare system at large [3]. The clinical manifestations of MS are diverse, with patients experiencing a range of deficits affecting physical (e.g., weakness, spasticity, sensory loss, ataxia), cognitive (e.g., memory), psychosocial, behavioural, and environmental aspects, all of which limit their activity and participation.

Spasticity in MS

Spasticity is defined as "a disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles" [4]. It affects nearly two-thirds of pwMS and poses significant management challenges due to the fluctuating and progressive nature of the disease [5]. The pathophysiology of spasticity is complex and not entirely understood. In the context of MS, it is believed to result from axonal degeneration or demyelination within specific descending tracts, or both, disrupting inhibitory inter-neuronal spinal network pathways [6]. MS-related spasticity can manifest as generalized, focal (affecting a localized part of a limb), or multifocal (affecting multiple parts of limbs). It causes stiffness and abnormal posturing of the limbs due to an imbalance of forces between agonist and antagonist muscles, affecting both static joint position and dynamic limb movement [7]. Truncal musculature can also be affected, leading to poor postural control. Spasticity is closely associated with disease progression, weakness, and fatigability. Additionally, adaptive features such as contractures and rheological changes in muscles, tendons, and joints may develop [8], further complicating limb positioning, movement, and overall function. Spasticity is a significant contributor to overall disability in pwMS [9]. The potential impact of spasticity-related problems in pwMS classified according to the World Health Organization (WHO) International Classification of Functioning, Disability and Health [10] at different levels is provided in Box 1.

Box 1. Potential impact of spasticity in persons with MS
- **Impairments:** Difficulties with body structures or physiological functions, such as restricted joint movement, loss of dexterity, abnormal limb postures, pain, etc.
- **Activity limitations:**
  - o Limitations in active limb use, affecting mobility , transfers, and activities of daily living, etc.
  - o Difficulties in pr oviding care to an affected limb, such as maintaining hygiene or applying a splint or orthotic.
- **Participation restrictions:** Limitations in societal roles related to family, work, and life situations.

Management of spasticity in pwMS

Managing spasticity in pwMS requires a comprehensive and individualized approach due to the multifaceted nature of MS. Patient-centred goals are collaboratively set by patients, caregivers, and the rehabilitation team, which typically focus on reducing symptoms, addressing impairments, improving activity levels (both active and passive functions), enhancing participation, and improving the quality of life (QoL) [11]. Currently, both non-pharmacological interventions and/or pharmacological agents are widely used for the management of spasticity [12-14]. Botulinum toxin A (BoNT-A) is often preferred for treating focal spasticity that does not respond well to non-pharmacological therapies [15]. Other antispasmodic medications commonly used include baclofen, diazepam, dantrolene, and tizanidine [9,16,17]. However, these medications have limited beneficial effects and are associated with high costs and systemic side effects [9,18,19].

Various non-pharmacological interventions are employed to manage spasticity in pwMS, including physical therapeutic modalities, electromagnetic therapies, whole-body vibration (WBV), acupuncture, etc. The effectiveness of these interventions varies among individuals, and often a combination of treatments is used within an interdisciplinary rehabilitation approach. Etoom et al. [20], in a systematic review, found mixed evidence for the benefits of physical therapy (PT) interventions

for spasticity in pwMS. The authors reported some evidence suggesting that exercise therapy, particularly robot-assisted gait training (RAGT) and outpatient exercise programs improved self-perceived spasticity and muscle tone, but there was no conclusive evidence for overall spasticity improvement [20]. Other non-pharmacological interventions, such as repetitive transcranial magnetic stimulation (rTMS), have shown a significant reduction in spasticity in the early post-intervention period (one week), but the evidence at follow-up (two weeks later) is insufficient [21]. Interventions like transcutaneous electrical nerve stimulation (TENS), transcranial direct current stimulation (tDCS), and WBV have not demonstrated additional benefits for spasticity in pwMS [13,22-24].

There is significant ambiguity about the benefits and risks associated with many non-pharmacological interventions. Despite guidelines and consensus statements advocating various non-pharmacological approaches to spasticity management [13,25], the evidence is largely based on isolated studies, narrative reviews, or expert opinions. A comprehensive systematic review published in 2013 (n=9 randomized controlled trials, RCTs), found limited evidence to support the effectiveness of non-pharmacological interventions, indicating a need for more rigorous studies [12]. Other published reviews in the area have reported diverse and sometimes conflicting conclusions [13,14,20,26-28]. This field is dynamic and constantly evolving. A systematic evaluation of the existing evidence is needed to clarify the effectiveness and safety of these non-pharmacological interventions and to inform clinical decision-making. Therefore, this review aims to systematically evaluate the literature to determine the effectiveness and safety of non-pharmacological interventions for managing spasticity in pwMS. Specific questions addressed include: Are non-pharmacological interventions effective in improving spasticity and spasticity-related impairments in pwMS? What specific types of non-pharmacological interventions are effective, and in which settings?

METHODS

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [29].

Literature search

A comprehensive search of the literature was undertaken using a multipronged approach, including search of health science databases: Cochrane Central Register of Controlled Trials (CENTRAL 2023, Issue 6), MEDLINE (PubMed), Embase (Embase.com), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO host); and clinical trial registries: ClinicalTrials.gov (www.clinicaltrials.gov); WHO International Clinical Trials Registry Platform (apps.who.int/trial search). The search strategy was adapted from our published protocol and review on the same topic [12], and run in all databases from June 2012 (search date of previous review) up to 14 April 2024. A manual search of bibliographies of pertinent articles, and a grey literature search were performed using different internet search engines and websites: such as System for Information on Grey Literature in Europe; New York Academy of Medicine Grey Literature Collection and Google Scholar. Furthermore, websites of various healthcare institutions; and governmental and non-governmental organizations associated with MS were searched and experts and researchers active in this field were contacted. No search limitations in terms of study outcomes, or methods of analysis were applied. Search strategies for each database are listed in Appendix 1.

Inclusion and exclusion criteria

All RCTs trialed in adult pwMS (18 years or over) with a confirmed diagnosis of MS (all subgroups) based on validated criteria [30-32] were included. All modalities of non-pharmacological interventions aimed at reducing (generalized, focal, or multifocal) spasticity in pwMS were considered, irrespective of settings (inpatient, outpatient, community rehabilitation centers or specialist rehabilitation centers; home-based settings, patients' own homes, etc.). Reference control groups considered included: no treatment; placebo/sham; waiting list conditions, or interventions given in different settings (ambulatory, inpatient, or home) and lower-intensity or different variants of intervention (e.g., lower dosage/intensity, different mode of delivery). Concomitant pharmacological/surgical interventions were accepted if they were run along with the non-pharmacological interventions in the same way in both the control and treated groups. The review did not consider surgical and pharmacological interventions provided in isolation for spasticity management.

Study selection

All studies identified through the search process and other sources were exported to an EndNote X9 (Clarivate) database to remove duplicates. Two review authors (BA, KS) screened and short-listed all abstracts and titles of studies identified by

the search strategy, based on the predefined selection criteria. Each potential study was independently evaluated, and the full-text article was obtained for assessment to determine the likelihood of inclusion. Any disagreement regarding the possible inclusion/exclusion of any individual study was resolved by consulting with the third author (FK). The final consensus decision was made by group discussion amongst all the authors. Additional information about the method of randomization or a complete description of the interventions from the trialists was sought when required.

Data extraction

All relevant data were extracted independently by two authors (BA, KS) using a standard proforma, which included: publication details; study design, date, sample size, participants' demographic and clinical characteristics, outcome measures; and details of intervention (type, intensity, settings, delivery mode, and duration). Further details were requested from the main author of the studies to obtain additional data and clarification when the provided data were not adequate or presented in graphs or figures format only. All disagreements were resolved by group consensus with the involvement of all review authors. All data were double-checked for any errors.

Assessment of methodological quality of included studies

The Cochrane Handbook for Systematic Reviews of Interventions was followed [33]. Two review authors (BA, KS) independently assessed the methodological quality of the included studies using the Cochrane 'Risk of bias' tool [33] according to the following domains: sequence generation (generation of allocation sequence); allocation concealment (concealment of allocation of participants to different groups); blinding (procedure of blinding of participants, personnel, and outcome assessors); incomplete outcome data (assessment of outcome data); selective outcome reporting (study free of any suggestion of selective outcome reporting); and other biases (other potential threats to validity). Based on predefined criteria, each domain was categorized as 'yes' (low risk of bias), 'no' (high risk of bias), and 'unclear' (either unclear or unknown risk of bias). Based on the judgment on these individual appraisal domains, the overall methodological quality of each study was rated into 3 levels: 'high-quality' (low risk of bias for all domains); 'low-quality' (unclear or high risk of bias for one or more domains) and 'very low-quality' (high risk of bias for most domains). Any disagreements were resolved by consensus among other review authors (MG, FK).

Measures of treatment effect

All data were entered and analysed using the Review Manager Web [34]. A quantitative analysis of the impact of the interventions was not possible due to clinical heterogeneity and a high amount of variability in terms of study methods, evaluated interventions (type, quantity, intensity) and control interventions, used outcome measures and assessment time points; and insufficient data. The certainty of the body of evidence for the spasticity outcomes was independently assessed by two authors (BA, KS) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool employing parameters: risk of bias, inconsistency, imprecision, indirectness, and publication bias [35]. The quality of evidence was graded as: "high" (very confident that the true effect lies close to that of the estimate of the effect); "moderate" (moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); "low" (confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect); and "very low" (very little confidence in the effect estimates and the true effect is likely to be substantially different from the estimate of the effect) [33,35]. Any disagreements were resolved through a consensus-based discussion among all authors.

RESULTS

A PRISMA flow diagram illustrating the study screening and selection process is presented in Fig. 1. A total of 2,943 titles and abstracts were retrieved from the search criteria (MEDLINE=360; Embase=714; CENTRAL=361; CINAHL=118; clinicaltrials.gov=899; Trial Registries via WHO Portal=491). An additional 14 articles were identified from other sources. After removing duplicates, 1,764 articles were screened, with 1683 excluded based on titles and abstracts. Consequently, 81 articles passed the initial screening and were selected for closer examination. The full text of these articles was assessed for further inclusion criteria, resulting in the final inclusion of 32 studies [22,24,36-65]. A total of 49 studies were excluded, with the main reasons for exclusion including: 24 studies not being RCTs, 18 studies lacking spasticity as a specific outcome measure, and 7 published protocols only (a list of excluded studies is detailed in Supplementary Table S1).

Characteristics of the included studies

Characteristics of the included studies are detailed in Table 1. In

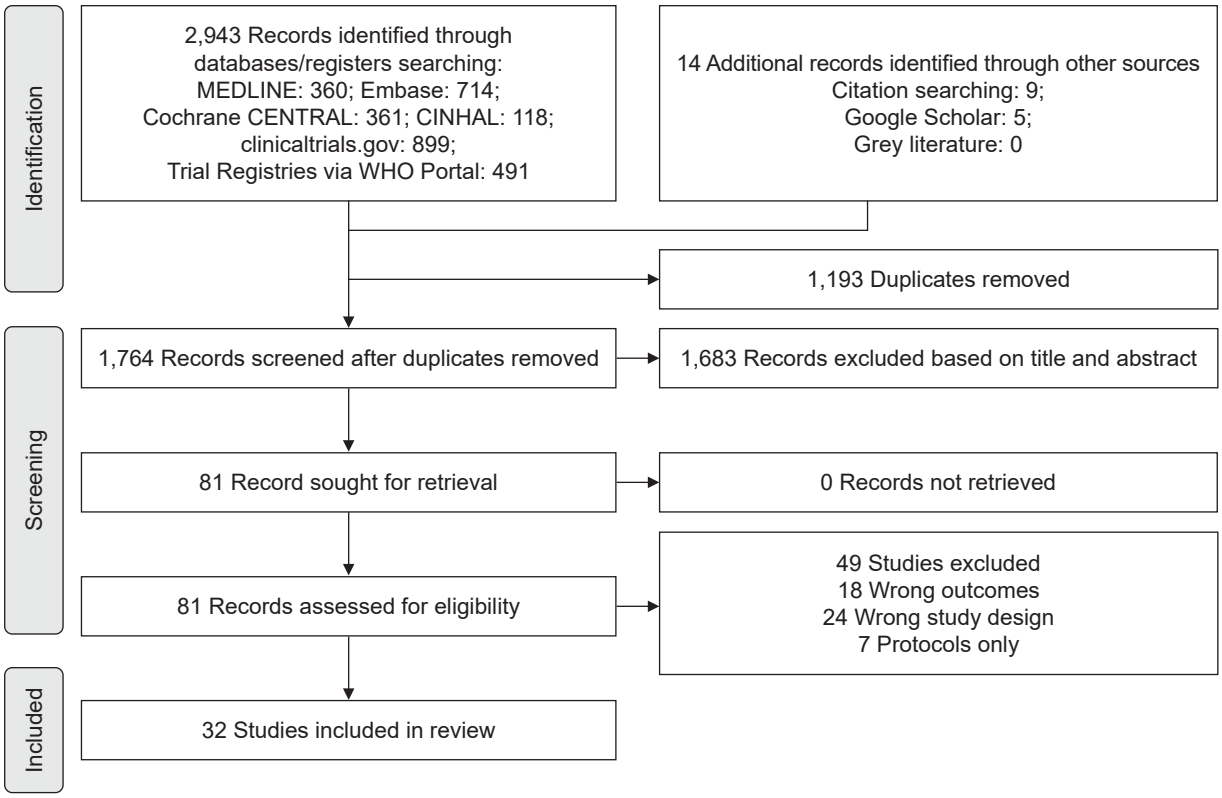

Fig. 1. PRISMA flow diagram showing a selection of article.

total, 32 RCTs involving a total of 1,481 participants were included. The studies highlighted diverse geographical distributions and a variety of non-pharmacological interventions [22,24,36-65]. Most studies were conducted in Europe (n=22), with six in Italy [40,47,50,54,55,58], three each in Turkey [38,60,62] and Austria [43,44,65], two in the United Kingdom [22,24], and one each in Slovenia [63], Denmark [57], Spain [37], France [39], Russia [52], and Germany [64]. Additionally, five studies each were conducted in Iran [36,42,46,56,61] and the United States [48,49,51,53,59], and one in Egypt [45]. Of the 32 included RCTs, four were of cross-over design [24,51,53,54], and one was conducted in two phases (open-label followed by an RCT) [44]. Only three trials were conducted in multiple centers [44,53,64].

Characteristics of the participants

All included studies recruited adult participants with a diagnosis of MS. The majority (n=19 trials) included all types of MS, while four studies exclusively included participants with RRMS [40,45,50,55], and three studies exclusively enrolled participants with SPMS [47,52,58]. The inclusion criteria varied between trials, with all including participants with definite MS, though only 18 trials specified commonly used clinical criteria. The majority (n=10) employed the McDonald criteria [38,41,45,50,52,54,55,58,62,65], four each used the Poser criteria [53,57,59,61], and Polman criteria [40,43,44,48]. The remaining 13 trials did not specify any criteria. All studies required some form of disability/impairment scale score within specified values as an entry criterion. The Expanded Disability Status Scale (EDSS) was the predominant measure used in 17 trials [36-40,45,48,50,51,54-56,58,62-65], followed by the Modified Ashworth Scale (MAS) in seven trials [22,41,46,47,52,57,60]. Four studies used both EDSS and MAS scores [38,39,54,61], two used Numeric Rating Scale (NRS) and EDSS scores [43,44], and one each used the Hauser Ambulation Index [24] and the MS Symptom Rating Form [53]. Two studies did not specify any scores in their selection criteria [42,59]. Most studies enrolled participants with lower limb spasticity.

Evaluated outcomes

Spasticity outcomes

A variety of outcome measures were employed to evaluate spasticity outcomes, and many used more than one tool. The mea-

Table 1. Characteristics and findings of included studies

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Physical therapeutic (exercise) program						
Abadi Marand et al., 2023 [36], Iran	N=64: TG=32, CG=32 TG: age=40.4±6.0 yr, M/F: 17/15, SPMS=21, RRMS=11, EDSS: 4.1±1.1, DD: 14.4±5.2 yr CG: age= 40.7±6.2 yr, M/F: 18/14, RRMS=10, SPMS=22, EDSS: 3.8±1.0, DD: 12.8±5.9 yr	TG: DNS exercises CG: CS Frequency: 15 60-min sessions 3 times per week for 5 weeks	Spasticity: MSSS-88, MAS Balance: BBS, postural stability Falls: falling rate; Fear of falling: activities-specific balance confidence, Biodex Balance System Trunk function: Trunk Impairment Scale Mobility: MSWS-12, TUG Baseline, post intervention (5 wk) & 17 wk	· Significant improvement in spasticity MSSS-88 at post-intervention & 17 weeks follow-up compared with the CS group, (group×time) (F=11.28, p>0.001) · No effect on MAS scores (p>0.05)	At post-intervention & 17 weeks significant improvement in DNS group compared with the CS group (group×time): · BBS (F=65.8, p<0.001) · Trunk Impairment Scale (F=40.6, p<0.001) · Postural stability (F=16.9, p<0.001) · Activities-specific balance confidence (F=10.1, p>0.001) · Reduced falling rate (F=9.0, p<0.001) · TUG (F=9.4, p<0.001) · MSWS-12 (F=3.8, p<0.05) · No AEs from both interventions	⊕⊕⊖⊖ Low
Andreu-Caravaca et al., 2022 [37], Spain	N=30: TG=18, CG=12 Age: 46.0±10.4 yr, M/F=15:15, RRMS=27, SPMS=3, EDSS: 3.2±1.5	TG: strength training (fast-velocity concentric) CG: usual care Frequency: 3 sessions/week on alternating days for 10 weeks	Spasticity: pendulum test Muscle activity: vastus lateralis (sEMG, peak sEMG), voluntary activation (central activation ratio), muscle contractile function Pre & post intervention (10 wk)	· Post-intervention significant improvement in spasticity, with differences between groups, in first swing excursion (right leg: p<0.01, ES=-1.4; left leg: p<0.05, ES=-1.2), number of oscillations (right leg: p=0.001, ES=-0.4; left leg: p<0.05, ES=-0.4) & duration of oscillations (left leg: p<0.01, ES=-0.6)	· Significant improvement with differences between groups in muscle activity (p<0.05, ES=-0.8) & maximal neural drive (p<0.05, ES=-0.8) · Voluntary muscle activation (central activation ratio) increased after intervention in IG (p<0.05, ES=-0.4) · Contractile properties remain unchanged in both groups · No AEs	⊕⊕⊖⊖ Low
Calabrò et al., 2017 [39], Italy	N=40 (RRMS): TG=20, CG=20 TG: age=44 (40–48) yr, M/F=7/13, EDSS: 4.4 (4–4.9), DD=11.5 (8–14) yr CG: age=41 (38–47) yr, M/F=8/12, EDSS: 4.75 (4.1–5.5), DD=11.5 (8–16) yr	TG: RAGT with VR CG: RAGT only Frequency: 5 sessions (30 min general conditioning+40 min RAGT) per week for 8 weeks	Spasticity: MAS Function & balance: TUG, BBS, FIM Cognition: COPE, HRSD Pre & post intervention (8 wk)	· No significant effect on spasticity between group (p>0.05, ES=-0.01, 95% CI=-0.5 to 0.5) or within group (p>0.05 for both groups)	· Non-significant difference between the groups for BBS (ES=-0.02, 95% CI=-2.4 to 2.4, p>0.05) & TUG (ES=-0.06, 95% CI=-0.4 to 0.5, p>0.05) · Significant moderate-to-large effect for positive attitude (ES=-0.5, 95% CI=-3.6 to 2.6) & problem-solving (ES=-0.9, 95% CI=-2.1 to 0.3, p<0.01) · No AEs	⊕⊕⊖⊖ Low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Eftekharsadat et al., 2015 [42], Iran	N=30: TG=15, CG=15 TG: age=33.4±8.1 yr, M/F=5/10, DD=5.8+3.9 yr CG: age=37.0±8.3 yr, M/F=3/12, DD=8.3+4.3 yr	TG: postural stability training program Biodex Balance System with VR CG: no intervention Frequency: 2 sessions (20 min) per week for 12 weeks	Spasticity: MAS Function & balance: MMT, TUG, Romberg test, BBS Fall risk & postural stability tests: FRI, and OSI Pre & post intervention	· No significant difference between groups on spasticity (MAS) scores of the knee & hip (p>0.05)	· Significant improvement in functioning but not in balance · No significant difference between groups on MMT scores of the wrist, hip, & knee, or BBS scores (p>0.05 for all) · Significant improvement in TUG scores in intervention group (p=0.01) · Significant improvement in FRI (p<0.001) & OSI (p<0.01) in intervention group · No report on AEs	⊕⊕⊖⊖ Low
Ergül et al., 2021 [46], Iran	N=26: TG=13, CG=13 TG: age=45.3±12.0 yr, M/F=7/5, DD=13.4±7.9 yr CG: age=43.8±7.6 yr, M/F=5/7, DD=13.4±7.9 yr	TG: SSE of hamstrings, quadriceps, hip adductors, plantar flexors muscles CG: FSE Frequency: 3 sessions (25–30 min) per week for 4 weeks	Spasticity: MAS Function: TUG, T25FWT, active ROM assessment Pain: VAS QOL: EQ-5D-5L Pre & post intervention (4 wk)	Significant reduction in spasticity in both groups (p<0.05), but no difference between groups In SSE group: · Strong correlation between decreased spasticity of quadriceps & improved function (TUG, r=0.7, p<0.01) · Strong correlation between decreased spasticity of quadriceps & improved walking (T25FWT, r=0.7, p<0.01) · Moderate correlation between decreased spasticity of hip adductors & improved strength (TUG, r=0.7, p<0.05) In the FSE group · Moderate correlations between decreased spasticity & increased ROM (r=0.7, p<0.05) & between increased ROM & functional improvement (p<0.05) · Strong correlation between decreased spasticity & increased HRQOL (p<0.01)	· Compared to baseline both groups showed significant improvement of functional tests, decrease of pain, increase of ROM & increase of HRQOL (p<0.05) · No significant differences between both groups in all variables before & after treatment (p>0.05) · No report on AEs	⊕⊕⊖⊖ Low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Giovannelli et al., 2007 [47], Italy	N=37: TG=20, CG=20 (18 at follow-up) TG: age=46.0±9.0 yr, M/F=2/18, EDSS: 5.8±1.3 CG: age=48.1±7.5 yr, M/F=2/16, EDSS: 6.0±1.1	BoNT & PT (passive or active exercise & a stretching regimen) Frequency: 40 min session daily/15 days after BoNT Control group: BoNT alone	Spasticity: MAS & VAS Function: EDSS Baseline, & weeks 2, 4, & 12	Significant decrease in MAS score in TG from baseline at (MD±SD): · Week 2: TG=-0.91±0.52, CG= -0.39±0.50, p<0.01 · Week 4: TG=-1.0±0.69, CG= -0.28±0.46, p<0.01 · Week 12: TG=-0.95±0.78, CG= -0.28±0.46, p<0.01 Mean (%) difference in MAS between baseline & 12 weeks: TG=-0.95 (26.1), CG=-0.28 (7.7) (p<0.01) Significant improvement in spasticity in VAS rating scale (MD± SD): · Week 2 to week 4: TG=1.77± (0.87), CG=0 (1.08), p<0.01 · Week 4 to week 12: TG=2.68 (1.08), CG=1.06 (1.16), p<0.01	· No adverse events post BoNT injections	⊕⊕⊖⊖ Low
Hugos et al., 2024 [49], USA	N=231: IG=115, CG=116 IG: age=53.7±12.1 yr, M/F=16/99, RRMS=64, PPMS=50, DD= 15.3 yr CG: age=55.1±11.1 yr, M/F=16/100, RRMS=54, PPMS=62, DD=17.0 yr	IG: STC: stretching exercise & education program CG: ROM exercises & education program Frequency: 2 h/wk classes; exercises: 15–30 mins/day	Spasticity: MSSS-88, NRS Function: MSWS, TUG, T25MW Fatigue: MFIS Others: PSQI, PROMIS (short form 8a), MSIS At 1 and 6 months	· No significant difference in MSSS scores between STC and ROM at 1 month (MD=0.28, 95% CI=-9.45 to 10.01, p>0.05) or 6-month (MD=-0.86, 95% CI=-12.2 to 10.5) · Significant improvements in group mean MSSS scores at 1 and 6 months in both groups	· Significant difference between groups in fatigue (MFIS, NRS) and impact of MS (MSIS) · No significant improvement in function (MSWS, TUG, T25FW)	⊕⊕⊖⊖ Low
Negahban et al., 2013 [56], Iran	N=48 (12 in each TGs & CG) TG I: age=36.3±7.6 yr, M/F: 2/10, EDSS=3.8±1.4, DD=48.7±97.1mts TG II: age=6.7±6.7 yr, M/F: 2/10, EDSS: 3.5±1.1, DD=102±81.1 mts TG III: age=36.7±7.6 yr, M/F: 2/10, EDSS: 3.6±1.4, DD=115.3±78.3 mts CG: age=36.8±8.7 yr, M/F: 2/10, EDSS=3.8±1.4, DD=86.6±34.3 mts	4 parallel groups: TG I: Swedish massage; TG II: exercises (strength, stretch, endurance & balance); TG III: combined massage & exercise CG: standard medical care Frequency: three 30 min sessions a week for 5 weeks	Spasticity: MAS (ankle plantar flexors) Pain: VAS Fatigue: FSS Function & gait/balance: BBS, TUG, 10MWT HRQOL: MSQLI-54 Pre & post intervention (5 wk)	· Significant improvement in MAS in TG I: MD±SD=0.54±0.6, p<0.01) & TG II: 0.47±0.7, p<0.05), but not in TG III: 014±0.8, p>0.05) · Significant worsening in MAS scores in CG: -0.33±0.5, p<0.05 · No significant difference between groups	· FSS scores improved in all TGs but worsened in CG · No significant difference in MSQL-54 between groups · Significant improvement in TUG in TG I (4.78±5.9, p<0.01 · TG I showed significantly larger change scores in all outcome measurements than the CG · TG II showed significant improvement in all outcomes except pain VAS scores than CG · No intolerance or the AEs of intervention	⊕⊕⊕⊖ Moderate

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Tarakci et al., 2013 [62], Turkey	N=110: TG=55, CG=55 TG: age=41.49±9.37 yr, M/F=17/34, EDSS: 4.38±1.37, DD: 9±4.71 yr CG: age=39.65±11.18, M/F=18/30, EDSS: 4.21±1.44, DD: 8.42±5.38 yr	Group exercise training including strength training, balance & coordination, core stabilisation, etc. Frequency: 3 sessions (1 h) a week for 12 weeks	Spasticity: MAS Function & balance: BBS, 10MWT, 10-steps climbing test Fatigue: FSS QOL: MSIQOL Pre & post intervention	Significant improvements in all lower limb spasticity (MAS scores) (p<0.05 for all) post-treatment: · R hip flexors: p<0.001, ES=1.01 · L hip flexors: p=0.015, ES=0.3 · R hamstring: p<0.001, ES= 0.92 · L hamstring: p<0.001, ES=0.8 · R Achilles: p<0.05, ES=0.54 · L Achilles: p<0.001, ES=0.95	Significant improvements in TG compared to CG: · Balance: BBS score increased 4.33 in the exercise group, while a decrease of 2.33 in CG (p<0.01) · Walking: 10MWT-decreased 2.72 seconds in TG, while increased by 1.44 in CG (p<0.001) · Reduction in fatigue: FSS score (<0.001) · Improve QOL: MusiQOL (p<0.05) · No AEs	⊕⊕⊕⊖ Moderate
Velikonja et al., 2010 [63], Slovenia	N=20: number of participants in each group not stated TG: (median): age=42, EDSS: 4.0 CG (median): age=41, EDSS: 4.2	TG: sports climbing (climbing wall, climbing belt and top rope system, climbing up and down wall) CG: yoga (stretching, strengthening exercises, breathing exercises, isometric muscle contraction & relaxation) Frequency: once a week for 10 weeks	Spasticity: MAS Function: EDSS Cognition: (executive function, attention span), Mazes subtest of Executive module from NAB, TOL, Brickenkamp d2 test Mood: CES-D Fatigue: MFIS Baseline & after treatment (10 wk)	· No significant improvements in spasticity after both interventions (p>0.05) · SC group had 25% reduction (p=0.046) in EDSS per year; before 4.0 (3.0–4.0) after 3.0 (2.5–4.0)	· Significant reduction in fatigue in TG (32.5%, p<0.05), while CG had no effect · Improved fatigue impact in TG before & after: MFIS 40.0 (36.5–53.0) to 27.0 (21.5–45.5), p<0.05 and MFIS cognition 17.0 (8.5–21.5) to 8.0 (6.0–19.5), p<0.05; MFIS physical 25.0 (21.5–28.5) to 19.0 (9.0–26.5), p<0.05 · No differences in executive function and mood · Increase in selective attention performance in the yoga group (17% increase; baseline: 151.0 (94.5–175.5); after: 176.5 (116.5–191.3; p<0.01) · No report on AEs	⊕⊖⊖⊖ Very low
Vermöhlen et al., 2018 [64], Germany	N=70: TG=32, CG=38 TG: age (Md, IQR)=50 (45–53), M/F=3/27; EDSS<5.0 in 33%, DD (Md, IQR): 16.5 (11–20) CG: age=51 (47–56), M/F=10/27, EDSS<5.0 in 30%, DD: 17.6 (11–27)	TG: hippotherapy & standard care CG: standard care Frequency: once a week for 12 weeks	Spasticity: NRS Balance: BBS Others: FSS, MSQOL-54, VAS pain scale Baseline, 6 weeks & 12 weeks	· Spasticity significantly improved in TG (NRS) from baseline to week 12: change from baseline=-1.7 points, no change in CG (-0.6), MD: -0.9 (95% CI: -1.9 to -0.1, p<0.05)	· Significant improvement in balance (BBS score, MD=2.33, 95% CI=0.03 to 4.63, p=0.047) · Benefit was largest for the subgroup with an EDSS≥5 (BBS score SD=5.1, p=0.001) · Significant improvement in fatigue (FSS score, MD=-6.8, p<0.05) · Significant improvement in QOL (MSQol-54, physical (MD=12, p<0.001) & mental health (MD=14.4, p<0.001) · 49 AEs (IG: 22 AEs in 13 patients, CG: 27 AEs in 15 patients); 3 serious AEs due to the necessary hospitalization (IG: 1 SAE [MS relapse], CG: 2 SAEs [MS relapse & infection])	⊕⊖⊖⊖ Very low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Zrzavy et al., 2021 [65], Austria	N=39: TG I=13, TG II=8, CG=11 TG I: age=43.9±6.2 yr, M/F=4/13, EDSS (MD, range): 4 (4–5), DD: 13±9 yr TG II: age=41.5±11.3 yr, M/F=4/7, EDSS=3.5 (2–5), DD=6±5 yr CG: age=43.9±6.1 yr, M/F=2/9, EDSS=6 (4–5), DD=14±7 yr	TG I: rehabilitation program+hypoxic endurance training TG II: rehabilitation program+normoxic endurance training CG: rehabilitation program Frequency (group 2 & 3): 45 minutes over 12 days (separated by a day without training)	Spasticity: MSSS-88 Fatigue: Erschöpfungsinventar bei Multipler Sklerose (WEIMuS), MFIS Walking: 6MWT Depressive symptoms: ADS Baseline, 7 days & 14 days	· Significant lower spasticity scores (MSSS-88) in both endurance training groups at 14 days (TG I: p=0.012; TG II: p<0.05) · Significant improvement in spasticity at 1 week in TG II (p<0.01) · No improvement in CG	· Significant improvement in walking endurance (6MWT) in TG I only at 14 days (p=0.001) · Fatigue scores improved significantly in all groups, but these improvements reached faster in TG I (p<0.01) & TG II (p=0.004) · No report on AEs	⊕⊕⊖⊖ Low
Magnetic brain stimulation						
Boutière et al., 2017 [39], France	N=17: TG= 9, CG=8 TG: age=48.2±9.4 yr, M/F=5/4, SPMS=6, RRMS=3, EDSS (Md, IQR): 6 (4–7), MAS: 7.6±4.7, DD: 12.2±8.2 yr CG: age=55.4±11.1 yr; M/F=4/4, SPMS=7, RRMS=1, EDSS=6 (6–6.5), MAS=5.6±2.7, DD=18.7±11 yr	TG: iTBS (10 bursts of 3 stimuli (50 Hz) repeated at theta frequency (5 Hz) every 10 seconds for a total of 600 stimuli (192 s) adjuncts to rehabilitation program CG=sham iTBS Frequency: once a day for 13 consecutive working days	Spasticity: MAS, VAS Brain function: resting-state fMRI Baseline, day after the last session of iTBS (week 3) & at the end of the 5-week rehabilitation program (week 5)	· Significant improvement in VAS spasticity score in iTBS group (p=0.026) · MAS score improved in both groups, but no significant difference between groups (p>0.05) · Changes in inter-hemispheric balance were correlated with improvement of spasticity (p<0.05)	· Significant effect of iTBS on the balance of the connectivity degree between the stimulated & the homologous primary motor cortex (p<0.01) · No effect of iTBS on global topology of brain network, suggesting that iTBS over the primary motor cortex does not alter global organization of brain network · No report on AEs	⊕⊕⊕⊖ Very low
Dieguez-Varela et al., 2019 [41], Spain	N=17: TG=10, CG=7 Age: 49.8±9.8 yr, M/F: 7/10, DD=12.4±6.4 yr	TG: iTBS (10 bursts with 3 pulses at 50 Hz repeated at 200 ms intervals (5 Hz) every 10 s for a total of 600 stimuli CG: sham stimulation Frequency: 10 daily sessions for 2 weeks	Spasticity: MAS, H/M amplitude ratio, PCS in the soleus muscle Assessments: immediately after 1 (S1), 5 (S5) & 10 (S10) sessions; 1 week (day 19) & 2 weeks after treatment	· No significant differences between the two groups in MAS & other clinical variables (PCS, adductor tone, joint balance, foot support & the Hauser ambulatory index) at any of the assessment time points · Significant decrease in H/M amplitude ratio from baseline (0.42±0.29) vs. S1 (0.35±0.25, p<0.05), vs. S5 (0.35±0.26, p<0.01) & vs. S10 (0.35±0 .27, p<0.01) · Effect was maintained up to 1 week after the last stimulation session: S1 (0.42±0.29) vs. day 19 (0.36±0.28), p<0.05 · No significant changes in CG	· AEs: 2 reported (subjective weakness in the right foot after the second session & a subsequent fall; & mild headache)	⊕⊕⊖⊖ Low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Korzhova et al., 2019 [52], Russia	N=34 SPMS: TG I: 12, TG II: 12, CG: 10 TG I: age=38 (29–54) yr, M/F=4/8, EDSS=6.5 (6–6.5) TG II: age=47 (43–53) yr, M/F=5/7, EDSS=6.5 (6–6.5) CG: age=45.0 (41–47) yr, M/F=5/5, EDSS=6.5 (6–6.5)	TG I: rTMS (20 Hz) & PT 45–55 min spastic muscle strengthening sessions TG II: iTBS CG: sham rTMS Frequency: 1 stimulation per day for 5 sessions for 2 weeks	Spasticity: MAS, SESS, NAS Fatigue: MFIS Other: pain level scale Baseline (T0), post intervention (T1, 10 sessions), 2 weeks (T2) & 12 weeks (T3)	· At T1, significant reduction MAS in both TG I (MD= -1.0, 95% CI: -1.3, -0.6, p<0.001), & TG II (MD=-1.5, 95% CI: -2.1, -0.8, p<0.001), but not in CG (MD= -0.2, p<0.05) · At T1 significant reduction of spasticity level as measured by SESS in both TG I: MD (95% CI)= -1.0 (-2.0, 0.0) & TG II: MD=-1.0 (-1.5, -0.5), but not in CG: MD=-0.5 (-1.3, 0.3) · At T1 significant reduction in NAS scores TG I: MD (95% CI=-2.8 (-4.0, -1.5), TG II: MD=1.6 (-2.9, -0.2), & CG=-1.3 (-2.3, -0.3) · At T3 significant reduction in SESS score only in iTBS group	· Significant reduction in pain in TG I only: MD (95% CI) =-5.0 (-8.6, -1.4) but not in TG II or CG · Significant reduction in MFIS score in TG I only: -7.0 (-11.7, -2.3), but not in TG II or CG · No AEs	⊕⊕⊕⊖ Moderate
Mori et al., 2011 [55], Italy	N=30: TG I: 10, TG II: 10, CG: 10 TG I: age=39.1±10.7 yr, M/F=7/3, EDSS=3.6±1.2 TG II: age 38.3±11.9 yr, M/F=5/5, EDSS=3.5±1.0 CG: age=37.7±12.3 yr, M/F=6/4, EDSS=3.8±1.6	TG I: iTBS (10 bursts, with each burst of 50 Hz 3 stimuli, repeated at a theta frequency of 5 Hz every 10 seconds, for a total of 600 stimuli (200 s) & exercise therapy TG II: iTBS alone CG: sham stimulation & exercise therapy Frequency: 10 bursts, 2 weeks	Spasticity: MAS, MSSS-88 Fatigue: FSS ADLs: BI HRQOL: MSQOL-54 Baseline & after treatment (2 wk)	Significant improvement in TG I: · MAS from the stimulated leg (2.1±0.4 before treatment; 1.3±0.4 after treatment; p<0.05) · MSSS-88 (74.3±11.4 before treatment; 53.2±10.9 after treatment; p<0.001) · In TG II, significant improvement in MAS (3.3±0.8 before treatment; 1.6±0.8 after treatment; p<0.05) · No significant changes in CG	Significant improvement in TG I on: · FSS (39.5±4.2 before treatment; 31.6±4.6 after treatment; p<0.05) · BI (92.5±2.4 before treatment; 95.0±1.85 after treatment; p<0.05) · MSQOL-54 physical health composite (59.7±2.7 before treatment; 64.8±2.7 after treatment; p<0.05) scores after treatment · None of the measured scales showed significant changes in CG · No report on AEs	⊕⊕⊖⊖ Low
Nielsen et al., 1996 [57], Denmark	N=38, TG: 21, CG: 17 TG: age=44 (34–67) yr, M/F=7/14, DD=12 (2–34) yr CG: age=44 (26–66) yr, M/F=5/12, DD: 13 (2–30) yr	TG: rTMS (1 25 Hz session of 16 stimuli over the leg motor area & 1 session of 5 Hz rTMS CG: sham stimulation Frequency: twice daily for 7 days	Spasticity: AS & Achilles tendon reflex grading scores; ease of ADLs (related to spasticity) Electrophysiological & biomechanical measurement: stretch reflex threshold Baseline & after treatment (1 day, 8 days, & 16 days)	At day 1 post-treatment: · AS score improved significantly in TG (MD= -3.3± 4.7 AU vs. 0.7± 2.5 AU, p<0.01) · Threshold of the stretch reflex significantly increased in TG (4.3±7.5 deg/s vs. -3.8±9.7 deg/s, p=0.001) At day 8 post-treatment · Threshold of the stretch reflex remain improved significantly in TG (4.4±7.5 deg/s vs. -1.8±8.5 deg/s, p<0.05) · No statistically significant difference in AS or self-score of ease of ADLs between groups At day 16 post-treatment · No statistically significant difference in any of the scores between two groups	· Significant improvement in self-score of ADLs in both groups · Self-score of ease of ADLs improved significantly in both groups on day 1 post-intervention (p<0.05 for both groups), but was no difference between the two groups · No report on AEs	⊕⊕⊖⊖ Low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Şan et al., 2019 [60], Turkey	N=16, TG=10, CG=6 TG: age=48.7±14.3 yr, M/F=6/4, DD=14.7±7.7 yr CG: age=53.0±8.8 yr, M/F=2/4, DD=19.5±10.9 yr	rTMS (5 Hz, 900 pulses over 15 minutes over vertex region targeting lower extremity motor area) CG: sham rTMS Frequency: 15 minutes for 10 sessions over 2 weeks	Spasticity: MAS, PSFS, Passive ROM Others: MSQOL-54, Epworth Sleepiness Scale, patient satisfaction, voiding diary Baseline, 1 week & 1 month after post-intervention	· Significant reductions in the MAS scores for the hip adductors bilaterally over time in TG ($p<0.01$), but no significant differences in CG ($p>0.05$) · Significant improvements in spasm (PSFS) in TG at both 1 week & 1 month ($p<0.01$), but no significant differences in the CG ($p>0.05$)	· Significant improvements in the rTMS group patient satisfaction, amount of urine leakage, actual health status, perceived health status, energy & fatigue, role limitations due to physical problems, social function ($p<0.05$ for all) · Significant improvement in overall QOL in TG (MSQOL-54) ($p<0.05$) · No AEs or complications were observed	⊕⊕⊖⊖ Low
Vibration therapy						
Ayvat et al., 2021 [38], Turkey	N=33: TG I=11, TG II=11, CG=11 TG I: age=37.7±9.7 yr, EDSS: 3.0±1.1, DD: 135.6±77.2 mo TG II: age=38.4±11.1 yr, EDSS: 2.75±1.0, DD= 84.0±56.9 mo CG: age=33.9±6.7 yr, EDSS=3.0±0.8, DD=127.0±84.4 mo	TG I: local vibration 50 Hz & exercise TG II: local vibration 100 Hz & exercise CG: exercise only Frequency: 1 hour a day for 3 sessions per week for 8 weeks	Spasticity: MAS Ankle joint position sense: isokinetic dynamometer Balance: Single Leg Stance Test & post-urographic assessment Gait: GAITRite Analysis System Baseline & post-treatment (8 wk)	· Significant decrease in spasticity & increase in fascicle length in TG I (both $p<0.05$) · No change in TG II and CG · No significant difference between groups	· Significantly improvement in ankle joint position sense, single-leg stance time, limits of stability/postural sway range in the mediolateral direction in both treatment groups (all $p<0.05$) · Significant improvement in antero-posterior limits of stability & postural sway in all groups (all $p<0.05$) · TG I showed significant improvement in all walking parameters & mediolateral limits of stability · Significant improvement in velocity, step length & base of support values in the TG II (all $p<0.05$) · Between group comparisons, significant difference was found only in mediolateral limits of stability ($p<0.05$) · CG showed significant improvement only for single support & stance phase percentages of the gait cycle (both $p<0.05$) · No report on AEs	⊕⊖⊖⊖ Very low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Paoloni et al., 2013 [58], Italy	N=48: TG I=14, TG II=14, CG=14 TG I: age=54.9±8.8 yr, M/F=6/8, EDSS: 5.3 (4–5.5) TG II: age=47.4±5.6 yr, M/F=5/9, EDSS: 4.8 (3.5–5.5) CG: age=50.6±8.9 yr, M/F=7/7, EDSS: 5.5 (4–6)	TG I: segmental muscle vibration (120 Hz) TG II: vibration & BoNT-A injection CG: BoNT-A injection Frequency: 30 min 3 times per week, over 4 weeks	Spasticity: MAS Fatigue: FSS ADLs: BI Baseline, 10 weeks & 22 weeks	· MAS score at knee & ankle significantly decreased over time (p<0.001) in all groups, but no differences between groups · Participants not receiving BoNT-A injection only displayed a significant increase in knee & ankle spasticity at 10 weeks (p<0.05)	· Significant reduction in fatigue (FSS scores) in vibration group & BoNT-injection only group at both 10 weeks & 22 weeks (p<0.05 for both), while no differences were detected in BoNT+vibration group · Significant improvement in spasticity in all participants · No differences in disability (BI) over time · No adverse events	⊕⊖⊖⊖ Very low
Schyns et al., 2009 [24], UK	N=16, TG I=8, TG II=8 Cross over design TG I: age=45.8±8.4 yr, M/F=3/5, DD: 6.7 yr (10 mo–23 yr) TG II: age=49.5±6.14 yr, M/F=1/7, DD=11.8 (3.5–11.8) yr	TG I: WBV 40 Hz, low amplitude (2 mm) for 30 seconds & stretching+strengthening exercise TG II: treatment in reverse order to TG I Frequency: 3 times/week for 4 weeks, 2 weeks no intervention & then 4 weeks of exercise alone	Spasticity, MAS, MSSS-88 Function: 10MWT, TUG Muscle force: dynamometer Sensation & proprioception: Nottingham sensory Assessment HRQOL: MSIS-29 Baseline & after treatment (4 wk) twice with 2 weeks cool off period	· No change in MAS scores for either intervention · Tone tended to increase more for exercise alone compared with whole body vibration & exercise · MSSS-88 spasm: greater reduction in score in TG compared CG (p<0.05, 95% CI=2.00, 14.50)	· Significant improvement in MSSS-88 scores pain (p=0.036) · No statistically significant changes for other MSSS-88 components (ADL, social functioning, stiffness, gait, body movement & emotional health) · No effects on sensation · Walking: both interventions increased the subjects' walking speed, no difference between groups (10MWT, p>0.05), (TUG, p>0.05) · MSIS-29: overall well-being improved in both groups, no statistically significant difference between groups (p<0.05) · No report on AEs	⊕⊖⊖⊖ Very low
Educational/self-management programs						
Ehling et al., 2017 [43], Austria	N=94: TG=47, CG=47 2 phases: open label followed by RCT TG: age=46.6 (43.2–50.1) yr, M/F=5/5, SPMS: 8, RRMS: 2, EDSS=4.2 (3.1–5.3), DD: 12.6 (8.8–16.5) yr CG: age=50.5 (44.6–56.5) yr, M/F=6/4, SPMS: 9, RRMS: 1, EDSS: 5.4 (4.2–6.5), DD: 16.3 (10.6–22.0) yr	Both groups received 4 weeks of inpatient MDR TG: 'MS-spasticity APP'-based exercises program CG: paper-based exercise program for 3 months, after 3-months all received MS-spasticity-based program for another 3 months	Spasticity: NRS, MAS, Spasm Frequency Score Muscle strength: Motricity Index Function: T25FWT, Others: self-rating scale for QOL, cognition, pain, fatigue Baseline, 12 weeks & 24 weeks	· No change in MAS scores · At 12 weeks, significant reduction in TG (NRS MD=1.2, p<0.05) · At 24 weeks, "MS-spasticity APP" was associated with a decrease in spasticity (NRS scores) in all participants (MD=2.5±1.7)	· No difference in QOL, strength, pain, fatigue & cognition	⊕⊖⊖⊖ Very low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Ehling et al., 2022 [44], Austria	N=94: TG=47, CG=47 TG: age=50.8 (41.8–57.9) yr, M/F=18/29, SPMS:13, RRMS: 26, PPMS: 8, EDSS: 5.0 (4–6), DD (median, IQR): 13.3 (10.1–22.7) yr CG: age=46.4 (41.7–55.5),; M/F=14/33, SPMS: 21, RRMS: 120, PPMS: 6, EDSS: 6.0 (4.5–6.5), DD: 12.5 (9.7–20.1) yr	MDR-inpatient (phase A) followed by TG: MS-Spasticity App delivered CG: paper-based exercise self-training program over 12 weeks (phase B)	Spasticity: NRS, MAS, Spasm Frequency Score Function: Motricity Index Balance: FSST Walking: T25FWT, 2MWD Fatigue: Würzburger Erschöpfungs-Inventar bei Multipler Sklerose Cognition: HADS, SF-36 Pre & post intervention	· Significant reduction in spasticity after MDR (NRS) (p<0.000), MAS (p<0.001), Spasm Frequency Score (p=0.001) · Superior effects on spasticity in the TG (median NRSs difference=-1.0, 95% CI=-1.7 to -0.3, p<0.01)	· MDR was also associated with significant improvements strength of lower extremities (p<0.001), & all mobility outcome measures (p<0.001) MS-Spasticity App was associated with: · Some improvement in balance (FSST) & walking distance (2MWD) · Significant reduction in cognitive fatigue (p<0.05), but no differences in levels of physical fatigue · Significantly higher exercise completion rate (92% vs. 72%, p<0.001)	⊕⊖⊖⊖ Very low
Hugos et al., 2017 [48], USA	N=40: TG=20, CG=20 TG: age=52.8±12.3 yr, M/F=7/13, SPMS: 6, RRMS: 10, PPMS: 3, EDSS: 4.8±1.1, DD: 15.1±8.1 yr CG: age=53.4±12.8 yr, M/F=4/16, SPMS: 4, RRMS: 8, PPMS: 7, EDSS: 4.9±1.5, DD: 15.7±10.5 yr	TG: group self-management program CG: usual care (stretching booklet & home stretching) Frequency: 2 hourly session & daily stretch for 4 weeks	Spasticity: MAS, MSSS-88 Function: TUG, T25FWT, 2MWD, MSWS-12 Cognition: MSIS-29, BDI-II Pre & post intervention	· No significant changes in MAS between TG & CG (MD=-1.6 vs. -1.4, p=0.953) · Significant improvement in MSSS-88 total scores in TG compared to CG (MD=-27.8 vs. -3.7, p<0.05); on the pain & discomfort subscale (MD=-3.9 vs. +0.3, p<0.05) & muscle spasms subscale (MD=-5.0 vs. -0.5, p<0.05)	· Significant improvement in TG in fatigue (MFIS p=0.03), depression (BDI-II, p=0.004), physical function (MSIS-29, p<0.01), & knowledge about spasticity on a written test (p<0.05) · No significant group difference (p>0.05) · No significant changes in physical tests	⊕⊖⊖⊖ Very low
tDCS						
El Habashy et al., 2022 [45], Egypt	N=20: TG=10, CG=10 TG: age=30±6.53 yr, EDSS=4.15±1.31, DD=3.70±3.09 yr CG: age=3.0±9.8 yr, EDSS=4.15±0.91, DD=4.30±3.47 yr	TG: anodal tDCS CG: sham tDCS Frequency: 1/daily session of 20-minute stimulation, 5 consecutive days	Spasticity: MAS, H latency, H/M amplitude ratio Before & after treatment (5 days)	· No significant differences in the MAS scores in both groups (p=0.22) · H/M amplitude ratio: TG showed significant improvement (0.6±0.2 vs. 0.5±0.1), no change in CG (0.6±0.2 vs. 0.6±0.2) · H latency: no difference in TG (30.8±2.8 vs. 30.3±2.6), but significant decreased in CG (32.9±2.6 vs. 31.9±2.6)	· No report on AEs	⊕⊖⊖⊖ Very low
Iodice et al., 2015 [50], Italy	N=20: TG=10, CG=10 TG: age=43.3±7.5 yr, M/F=2/8, EDSS: 3.6±0.9, DD=7.0±3.1 yr CG: age=40.3±4.5 yrs, M/F=3/7, EDSS: 3.8±0.9, DD=7.8±1.9 yr	TG: anodal tDCS (2 mA to primary motor cortex of the more affected side) CG: sham tDCS Frequency: 20 min/day for 5 days	Spasticity: MAS, MSSS-88 Function: MSWS-12 Baseline & post-intervention (5 days)	· No significant interaction for spasticity scales: MAS (p>0.05); MSSS-88 (p>0.05) · No significant differences between the two groups post-intervention: MAS, MSSS-88 (p>0.05 for both)	· No significant changes in walking in both groups (MSWS-12, p>0.05) · No group difference (MSWS-12, p>0.05) · No AEs	⊕⊖⊖⊖ Very low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Pulsed electromagnetic device						
Lappin et al., 2003 [53], USA	N=117 multisite cross-over design, all underwent treatment device alternating with control device and vice versa Age (range)=21–64, M/F=28/89, SPMS: 27, RRMS: 52, PPMS: 12, DD (range)=1 to >13 yr	TG: PEM device CG: placebo Frequency: 4 weeks for up to 24 h/day), separated by a 2-week washout period	MSQLI: fatigue, pain, spasm/spasticity, bladder control, QOL Function: MS Performance scales; MS Rating Form and Mobility Index Baseline, after 4-week treatment & 10 weeks	· No significant reduction in spasticity · Significant improvement in spasms (MD=-0.13; p<0.05) · No further data or analysis reported for spasms/spasticity	· Significantly greater Improvement in fatigue & overall QOL · No significant differences in the treatment effects for bladder control (p>0.05) (MSQLI) & disability composite (p>0.05) (MSPS) · 3 scales (fatigue, pain & spasticity) used to create the QOL index (QLI) showed moderate inter-correlations (r=0.32 to 0.60), however, bladder control scale showed poor correlation with other MSQLI scales (r=0.00 to 0.26) · No report on AEs	⊕⊖⊖⊖ Very low
Richards et al., 1997 [59], USA	N=30: TG=15, CG=15 TG: M/F=8/11, SPMS or PPMS: 8, RRMS: 7, EDSS: 5.1 (0–9) CG: M/F=5/10, SPMS or PPMS: 10, RRMS: 5, EDSS: 4.98 (0–8.5)	TG: magnetic pulsing device (Enermed), range: 4–13 Hz (50–100 milliCauss) CG: sham device Frequency: 10–24 hours a day for 2 months	Patient-reported performance scale-symptoms: spasticity, bladder control, cognitive level, fatigue level, hand function, mobility, sensation, vision Function: EDSS brain electric activity: quantitative EEG during a language task) Baseline & after treatment (2 mo)	· Significant difference between pre-treatment & post treatment within the treatment group in spasticity: MD=-0.80±0.23; p<0.01 · No difference between group	· No significant change in EDSS scale · Significant improvement in the performance scale combined rating for: bladder control, cognition, fatigue, mobility, vision (p<0.05 for all) · Significant change between pre-treatment & post-treatment in alpha EEG magnitude during the language task · 19 AEs reported (11 in intervention group & 8 in control group)	⊕⊖⊖⊖ Very low
TENS						
Miller et al., 2007 [22], UK	N=32: TG=16, CG=16 Cross-over design Demographic not reported	TENS (100 Hz, 0.125 ms pulse width)-60 minutes vs. 8 hours Frequency: 2 weeks of 60 minutes (period A) & 8 hours daily (period B) followed by 2 weeks washout period	Baseline & after (2 wk) treatments; & follow-up (8–20 mo) for the questionnaires for patient report for symptoms	· No statistically significant differences in the Global Spasticity Score following either 60 minutes or 8 hours daily of TENS (p>0.05 for both) · 8-hour TENS compared with 60 minutes led to significant reduction in muscle spasm (p<0.05) & pain (p<0.01)	· At the end of the study (8–20 mo) patients reported reduction in symptoms: 87.5% for spasm, 73.3% for pain & 73.3% for stiffness · No report on AEs	⊕⊖⊖⊖ Very low

(Continued to the next page)

Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Shaygannejad et al., 2013 [61], Iran	N=58: TG=28, CG=30 TG: age=39.5±9.3 yr, M/F=9/17, SPMS: 5, RRMS: 20, PPMS: 1, EDSS: 2.1±1.4, DD: 7.2±5.0 yr CG: age=38.9±7.8 yr, M/F=6/12, SPMS: 8, RRMS: 18, PPMS: 0, EDSS: 2.6±1.3, DD: 5.3±2.8 yr	TG: TENS (100 Hz, with pulse width set at 250 ps) 20–30 minutes CG: baclofen (10 mg twice daily, increasing over 3 weeks to 25 mg) Frequency: 4-week	Spasticity: MAS Baseline & 4 weeks	· Significant reduction in MAS score at 4 weeks in both groups (TG MD=-1.04, CG: MD=-0.58, p<0.001 for both) · MAS scores significantly lower in TG at 4 weeks than CG (MD=-0.42, p<0.05)	· Four participants from the baclofen group dropped out due to AEs	⊕⊖⊖⊖ Very low
Shock wave therapy						
Marinelli et al., 2015 [54], Italy	N=68: TG=34, CG=34 TG: age=51.7± 11.3 yr, M/F=14/20, EDSS: 6.6± 0.8 CG: age=51.00±13.2 yr, M/F=16/18, EDSS: 6.2±1.2	TG: RSWT over ankle extensor muscles (4 Hz frequency, with a pressure of 1.5 Bars, 2,000 shots) CG: placebo RSWT Frequency: 4-session course, with a 1-week interval between sessions	Spasticity: MAS Spinal excitability: H-reflex Pain: VAS Ankle strength: Medical Research Council rating Walking: 10MWT Baseline; 1 week after the first session; & 4 weeks after last session	· MAS scores significantly decreased only at 1 week (MD=-0.78, p<0.0001) · No changes at 4 weeks · No significant changes in H-reflex compared to healthy controls	· Significant reduction in pain VAS scores at all follow-up assessments, with the maximal effect at 1 week (MD= 3.05, p<0.0001) · No significant changes in ankle strength & walking · Spinal excitability was unaffected · No significant changes in any of the parameters in CG · No AEs	⊕⊖⊖⊖ Very low
Complementary and alternative medicine						
Karpatkin et al., 2023 [51], USA	N=12: TG=6, CG=6 Crossover design Age=52.7±16.3 yr, M/F=6/6, SPMS: 2, RRMS: 9, PPMS: 1, EDSS: 3.4±0.76	TG: acupuncture CG: no treatment Frequency: twice weekly for 4 weeks, followed by a 1-week washout period, & then crossed over to the other condition for 4 weeks	Spasticity: MAS Gait & balance: 6MWT, T25FWT, Mini-Balance Evaluation System Test Strength: handheld dynamometer Sensory testing: Biothesio meter Baseline & post intervention	· Significant improvement in spasticity (MAS) score in right hip flexors (p<0.05) · Other lower limb muscles were unaffected (p>0.05 for all)	· No statistically significant changes were observed in the gait or balance measures · Small statistically significant changes were observed in upper extremity strength · No changes in sensation · No AEs	⊕⊖⊖⊖ Very low

GRADE, Grading of Recommendations Assessment, Development and Evaluation; TG, treatment group; CG, control group; M/F, male/female; EDSS, Expanded Disability Status Scale; DD, disease duration; MS, multiple sclerosis; RRMS, relapsing-remitting MS; DNS, dynamic neuromuscular stabilization; CS, core stabilization exercises; MSSS-88, MS Spasticity Scale-88; MAS, Modified Ashworth Scale; BBS, Berg Balance Scale; MSWS, MS Walking Scale; TUG, Timed Up and Go; AE, adverse event; sEMG, surface electromyography; ES, effect size; IG, intervention group; RAGT, robot-assisted gait training; VR, virtual reality; FIM, Functional Independence Measure; COPE, Coping Orientation to Problem Experienced; HRSD, Hamilton Rating Scale for Depression; CI, confidence interval; MMT, Manual Muscle Test; FRI, Fall Risk Index; OSI, Overall Stability Index; SSE, static stretching exercise; FSE, functional stretching exercise; T25FWT, Timed 25-Foot Walk Test; ROM, range of motion; VAS, visual analogue scale; QOL, quality of life; HRQOL, health-related QOL; BoNT, botulinum toxin; PT, physiotherapy; MD, mean difference; SD, standard difference; PPMS, primary progressive MS; STC, Spasticity: Take Control; NRS, Numeric Rating Scale; MFIS, Modified Fatigue Impact Scale; PSQI, Pittsburgh Sleep Quality Index; PROMIS, Patient-Reported Outcomes Measurement Information System; MSIS, MS Impact Scale; 10MWT, 10-Meter Walk Test; MSQLI, MS QOL Inventory; FSS, Fatigue Severity Scale; MSQOL-54, Multiple Sclerosis QOL-54 Scale; MSIQOL, MS International QOL; NAB, neuropsychological assessment battery; TOL, Tower of London Test; CES-D, Center for Epidemiologic Studies Depression Scale; MSQOL, MS QOL Scale; 6MWT, 6-Meter Walking Test; ADS, Allgemeine Depressionsskala; SPMS, secondary progressive MS; iTBS, intermittent theta burst stimulation; fMRI, functional magnetic resonance imaging; PCS, cortical silent period; rTMS, repetitive transcranial magnetic stimulation; SESS, Subjective Evaluating Spasticity Scale; NAS, Numerical Analog Scale; AS, Ashworth Scale; ADLs, activities of daily living; BI, Barthel Index; PSFS, Penn Spasm Frequency Scale; WBV, whole body vibration; RCT, randomized controlled trial; MDR, multi-disciplinary rehabilitation; FSST, Four Square Step Test; 2MWD, 2 meter walking distance; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form-36; BDI-II, Beck Depression Inventory; tDCS, transcranial direct current stimulation; MSPS, MS Performance Scale; EEG, electroencephalogram; TENS, transcutaneous electric nerve stimulation; RSWT, radial shock wave therapy.

surement tools employed to assess the spasticity outcomes included followings: MAS-most frequently utilized (n=21 studies) [36,38-40,42,44-48,50-56,58,61-63]; Multiple Sclerosis Spasticity Scale (MSSS-88, n=7 studies) [24,36,48-50,55,65]; electrophysiological parameters (H-reflex excitability, electromyography [EMG] muscle activity) (n=3 studies) [41,45,54]; NRS (n=4 studies) [43,44,49,64]; visual analogue scale (VAS) (n=2 studies) [39,47]; pendulum test for muscle tone (n=1 study) [37]; Spasm Frequency Score (n=1 study) [44]; Patellar Tendon Reflex Scale (n=1 study) [24]; Penn Spasm Frequency Score (n=1 study) [60]; Global Spasticity Scales (n=1 study) [22]; Subjective Evaluating Spasticity Scale (SESS) (n=1 study) [52]; other assessment tools such as patient self-reported scores [57,59].

Other outcomes

Other commonly assessed outcomes included balance, fatigue, mobility, gait/walking speed, overall function, cognition, QoL, pain, and others. The recruitment period was not disclosed in any of the studies. Follow-up periods varied across trials, with most evaluations occurring immediately after treatment or within two weeks. Only two trials reported a long-term follow-up, ranging from eight to 20 months, focusing solely on patient-reported symptoms using subjective questionnaires [22,49].

Quality assessment of included studies

The authors' judgments of each item presented as percentages across all included studies are presented in Fig. 2 and the assessment of methodological quality is shown in Fig. 3. The methodological quality of the 32 included trials was generally low, with substantial flaws and a high risk of bias in at least one domain. Key issues included randomization procedures, blinding of participants, therapists, and outcome assessors, small sample sizes, and outcome analysis. Although all included studies stated they used randomization, fewer than half (15 studies) adequately reported their methods of randomization. Many studies did not provide sufficient details on the generation and concealment of the random allocation sequence. Only 10 studies described and implemented adequate concealment of allocation prior to study entry [40,46,53,56-59,61,62,65], while three did not report on this aspect [22,48,49], and the remaining studies had incomplete reporting on sequence generation methods.

Adequate blinding of participants and treating personnel was reported in only seven studies [46,48,53,54,57,59,65]. Seventeen studies did not implement blinding [22,24,36-38,40,42,47,49-51,56,58,61-64], and the blinding status was unclear in the remaining studies. Variability in attrition was observed, with the majority of studies reporting no participant withdrawals or lost follow-ups. However, eight studies had substantial dropout rates [24,38,43,44,51,53,62,65], leading to a high risk of bias due to small sample sizes and the potential impact of dropouts on results. One study [63] provided no information on attrition, while three studies only reported the total number of dropouts without specifying treatment arms [22,51,53]. Selective reporting bias was not evident, as all studies reported pre-specified primary and secondary outcomes. However, 14 studies had small sample sizes (≤30 participants) and were not adequately powered [24,37,39,41-43,45,46,50,51,55,59,60,63]. Furthermore, thirteen studies did not utilize a conventional control group but employed comparative control groups involving another non-pharmacological intervention [24,36,38,40,43,44,46,49,63,65] or pharmacological interventions [47,58,62]. Most studies had short-term follow-ups, with assessments limited to immediate post-treatment evaluations.

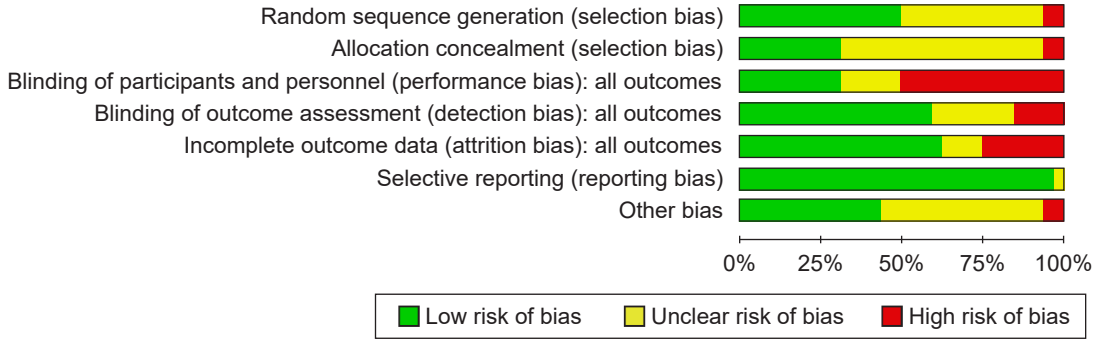

Fig. 2. Risk of bias graph.

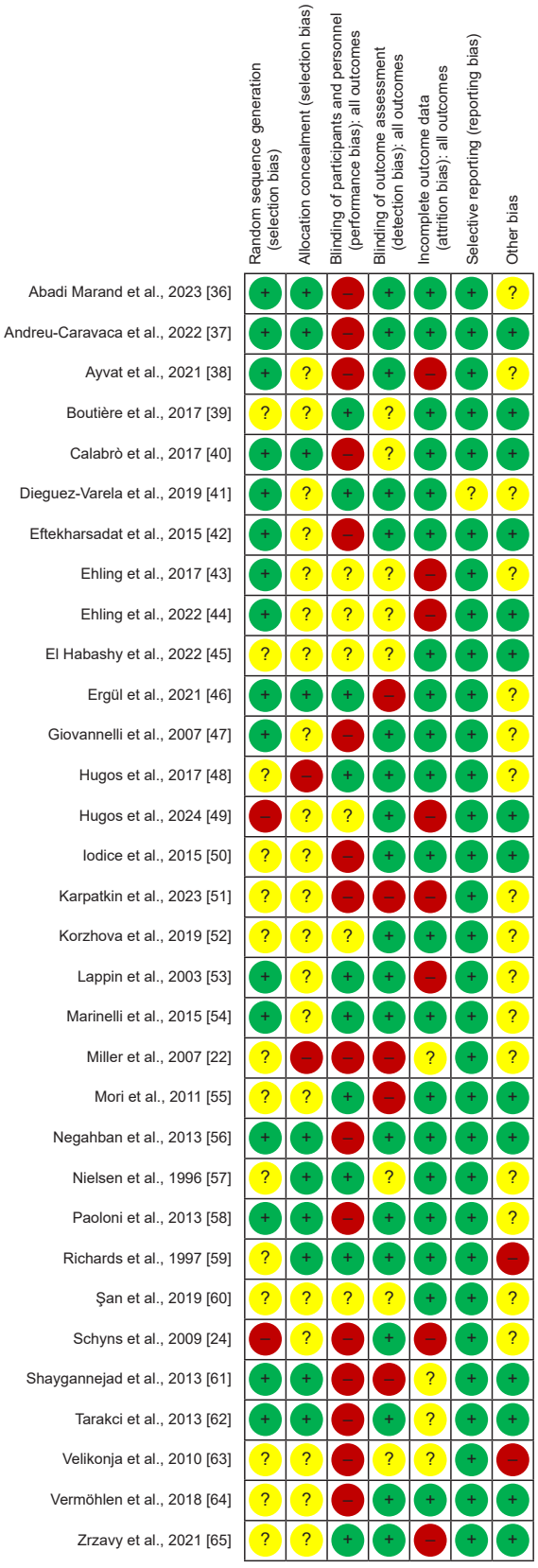

Fig. 3. Risk of bias summary.

Effects of interventions

A diverse array of non-pharmacological interventions was evaluated in the included studies, which underscores the intricate nature of non-pharmacological approaches in addressing the multifaceted effects of spasticity in this patient population. Many of these interventions are frequently employed in conjunction with other treatments, including pharmacological therapy or additional non-pharmacological interventions. The non-pharmacological interventions assessed in the included studies fall into nine primary categories, based on their mode of application (APP): physical therapeutic programs, magnetic brain stimulation (rTMS, intermittent theta burst stimulation [iTBS]), tDCS, pulsed electromagnetic field (PEMF) devices, TENS, vibration therapy, shock wave therapy, educational and self-management programs, and complementary and alternative medicine (CAM). The summary of the findings is presented below and detailed in Table 1.

Physical therapeutic programs

Twelve studies evaluated the impact of diverse physical activity programs on individuals with various forms of MS. These programs encompass structured physiotherapy, exercise regimens, stretching, balance and coordination exercises, postural stabilization, sports climbing, hippotherapy, RAGT, and others [36,37,40,42,46,47,49,56,62-65]. The effectiveness of these modalities varied, and they were often used in combination with other approaches.

Giovannelli et al. [47] evaluated (n=38 SPMS) the efficacy of combining PT with BoNT-A injections for managing focal spasticity. The intervention group received BoNT-A injections and daily PT (passive or active exercise and stretching regimens) for 15 days, while the control group received only the BoNT injections. The treatment group showed significant reductions in spasticity, as measured by the MAS, compared to the control group at weeks two (2.73 vs. 3.22), four (2.64 vs. 3.33), and twelve (2.68 vs. 3.33) ($p<0.01$ for all time points). Further, there was a significant improvement in MAS scores from baseline to the end of the 12-week follow-up in the treatment group (mean difference [MD]=-0.95 vs. -0.28, $p<0.01$). The intervention group also showed superior efficacy in reducing spasticity symptoms, as measured by the VAS, at week four (6.95 vs. 5.50, $p<0.01$) [47].

A RCT by Zrzavy et al. [65] (n=39 pwMS) allocated participants into three parallel groups: a routine clinical rehabilitation program combined with either hypoxic or normoxic endur-

ance training, and a control group with rehabilitation program only. The study found significantly lower spasticity scores, as measured by the MSSS-88, in both the hypoxic and normoxic endurance training groups at 14 days (p=0.012 and 0.048, respectively). Remarkably, a significant reduction in spasticity was observed after just one week of hypoxic endurance training (p=0.009). Additionally, all groups showed significant improvements in fatigue scores, with faster improvements in the endurance training groups (p=0.004 for normoxic and p=0.002 for hypoxic). Only the hypoxic group demonstrated a significant improvement in walking speed (p=0.001) [65].

A RCT with a wait-list control group (n=110 pwMS) evaluated the efficacy of a 12-week (36 sessions) physical therapist supervised group exercise program involving flexibility, strength training, balance and coordination exercises, core stabilization, and functional activities [62]. all by a. Post-treatment, significant improvements in lower limb spasticity were observed in the exercise group (MAS scores, p<0.05). Additionally, the exercise group showed significant improvements in balance (Berg Balance Scale [BBS] score increased by 4.33 points, compared to a decrease of 2.33 points in the control group, p=0.003) and walking ability (10-meter walk test time decreased by 2.72 seconds in the exercise group, compared to an increase of 1.44 seconds in the control group, p<0.001). The intervention group also experienced significant improvements in fatigue and QoL (p<0.001 and p=0.006, respectively) [62].

Another RCT (n=30 pwMS) examined the effects of 10 weeks of strength training on voluntary activation, muscle activity, muscle contractile properties, and spasticity [37]. There were significant improvements in spasticity in the strength training group, with notable differences between groups after the intervention. Specific parameters showing improvement included first swing excursion (right leg: p=0.006, effect size [ES]=-1.4; left leg: p=0.031, ES=-1.2), number of oscillations (right leg: p=0.001, ES=-0.4; left leg: p=0.031, ES=-0.4), and duration of oscillations (left leg: p=0.002, ES=-0.6). Additionally, significant improvements were observed in muscle activity (p=0.031, ES=-0.8) and maximal neural drive (p=0.038, ES=-0.8). Voluntary muscle activation, measured by the central activation ratio, also increased in the strength training group (p=0.010, ES=-0.4). However, there were no changes in muscle contractile properties in either group [37].

One RCT (n=30 participants with RRMS or SPMS) evaluated the efficacy of a short-term virtual reality (VR)-based balance training program on patients' balance ability, compared to a control group with no intervention [42]. The study found no significant difference between the groups in spasticity scores for the knee and hip (MAS, p>0.05). However, the intervention group showed significant improvements in mobility (Timed Up and Go [TUG] scores, p=0.01), an increased ability to maintain stability (Overall Stability Index, p=0.005), and a reduced risk of falls (Fall Risk Index, p<0.001). The authors found no significant differences between the groups in muscle power and balance (p>0.05 for all) [42].

Another RCT (n=64 pwMS) evaluated the effects of core stabilization and dynamic neuromuscular stabilization on balance, trunk function, mobility, falling, and spasticity [36]. The findings revealed a significant improvement in spasticity, at both post-intervention and 17-week follow-up in the dynamic neuromuscular stabilization group compared to the core stabilization group (group×time inter action, p>0.001). However, there was no significant difference in MAS scores between the groups (p>0.05). Further, compared to the core stabilization group, the dynamic neuromuscular stabilization group exhibited significant enhancements in balance (BBS, Trunk Impairment Scale, postural stability, activities-specific balance confidence), reduced falling rate, and improved mobility (TUG test, and MS Walking Scale-12, p<0.0001) [36].

One RCT (n=40 pwMS with walking disabilities) investigated the efficacy of RAGT with or without a VR system over 8 weeks [40]. The authors found no significant effect on spasticity (p=0.4, ES=-0.011), and there was a non-significant difference between the groups regarding balance (BBS, p=0.8) and mobility (TUG, p=0.3). However, there was a significant moderate-to-large effect observed mainly favouring RAGT with the VR group for the positive attitude (p=0.005) and problem-solving (p=0.002) sub-items of the Coping Orientation to Problem Experienced scale [40].

Ergül et al. [46] 2021 conducted an RCT (n=26 pwMS) comparing the effects of static stretching exercise (SSE) and functional stretching exercise (FSE) over 4 weeks (12 sessions) on lower limb spasticity, function, lower limb pain, active range of motion (ROM), and health-related quality of life (HRQOL). All participants underwent stretching exercises targeting the hamstrings, quadriceps, hip adductors, and plantar flexor muscles. Both groups exhibited significant improvements compared to baseline, including decreased spasticity, enhanced functional tests, reduced pain, increased ROM, and improved HRQOL (p<0.05 for all). However, there were no significant differences between the groups in any of these variables before or after

treatment (p>0.05). In the SSE group, a strong correlation was observed between decreased spasticity and functional improvement (r=0.793, p=0.002), while in the FSE group, moderate correlations were found between decreased spasticity and increased ROM (r=0.689, p=0.013) and increased ROM and functional improvement (r=0.593, p=0.042). Additionally, a strong correlation was identified between decreased spasticity and increased HRQOL in the FSE group (r=0.721, p=0.006) [46].

Negahban et al. [56] (n=48 participants) explored the comparative effects of exercise programs (strength, stretch, endurance, and balance) and Swedish massage. Participants were randomly assigned into four equal subgroups: massage therapy, exercise therapy, combined massage and exercise therapy, and control group (standard medical care). The authors found that both massage therapy and exercise therapy resulted in significant improvement in MAS scores (MD=0.05, p=0.006 and MD=0.47, p=0.031, respectively). However, there was no significant improvement in the massage and exercise combination group (MD=0.14, p=0.53) and significant worsening in the control group (MD=-0.33, p=0.031). The massage therapy also resulted in a significantly larger improvement in pain reduction (MD=2.75 points, p=0.001), dynamic balance (MD=3.69 seconds, p=0.009) and walking speed (MD=7.84 seconds, p=0.007) than exercise therapy. Further, patients in the combined massage and exercise therapy showed significantly larger improvement in pain reduction than those in the exercise therapy (MD=1.67 points, p=0.001) [56].

Velikonja et al. [63] (n=20 participants with RRMS and PPMS) explored the effects of two 10-week contemporary aerobic physical activities, sports climbing, and yoga. Both activities involved a series of stretching techniques that required body control and planning of complex movements. The study found no significant improvements in spasticity following either intervention. However, the sports climbing group experienced a notable 25% reduction in the EDSS pyramidal function score post-treatment (p=0.046). In contrast, the yoga group showed a significant 17% improvement in selective attention performance post-treatment (p=0.005). Further, the sports climbing group demonstrated a substantial 32.5% decrease in fatigue (p=0.015), whereas yoga did not have any effect on fatigue levels [63].

A multi-center RCT (n=70 pwMS) examined the impact of an additional 12 weeks of hippotherapy alongside standard care (control group) [64]. There was a significant improvement in spasticity in the intervention group at 12 weeks (NRS, MD=-0.9, 95% confidence interval [CI]: -1.9 to -0.1, p=0.031). Additionally, significant improvements were observed in the treatment group for balance (BBS score, p=0.047), with the most substantial benefit seen in patients with an EDSS score of ≥5 (BBS score, p=0.001). There was also a significant reduction in fatigue (Fatigue Severity Scale [FSS] score, p=0.02) in the intervention group. Further, improvements were noted in the QoL of participants in the intervention group, both in terms of physical (SD=12, p<0.001) and mental health (SD=14.4, p<0.001) [64].

One most recent RCT (n=231 participants) evaluated the impact of a guideline-based program of spasticity education and stretching exercises "MS Spasticity: Take Control (STC)" compared to a control program of different spasticity education and ROM exercises in ambulatory pwMS [49]. The authors found significant improvements in spasticity and fatigue, and psychological scores at 1 and 6 months in both groups. However, there was no significant difference between STC and ROM at 1 month (MSSS scores MD=0.28, 95% CI=-9.45 to 10.01, p=0.955) or 6-month (MD=-0.86, 95% CI=-12.2 to 10.5) [49].

Magnetic brain stimulation

TMS is a non-invasive neurostimulation technique that uses electromagnetic induction to generate electric currents in the brain. Six studies evaluated the effectiveness of various types of rTMS, each with its specific parameters and APPs: two studies evaluated the efficacy of iTBS [39,55], three studies assessed rTMS [41,57,60], and one study compared rTMS with iTBS [52].

A double-blind, sham-controlled trial (n=30 pwMS) investigated the impact of combining iTBS with exercise therapy on motor disability [55]. Participants were randomly assigned into three groups: iTBS plus exercise therapy, sham stimulation plus exercise therapy, and iTBS alone. Significant improvements in spasticity were observed in the iTBS plus exercise therapy group, with MAS scores decreasing from 2.1±0.4 before treatment to 1.3±0.4 after treatment (p<0.05) and MSSS-88 scores decreasing from 74.3±11.4 to 53.2±10.9 (p<0.001). The iTBS alone group also showed a significant reduction in MAS scores, from 3.3±0.8 before treatment to 1.6±0.8 after treatment (p<0.05), while other measures of MS-related disability remained unaffected. Furthermore, the iTBS plus exercise therapy group experienced significant improvements in fatigue (FSS scores), daily function (Barthel Index scores), and QoL (Multiple Sclerosis Quality of Life-54 Scale physical health composite scores), with all showing significant improvement compared to the sham stimulation plus exercise therapy group (p<0.05 for all) [55].

Boutière et al. [39] in a RCT (n=17 pwMS) investigated whether the modulation of spasticity induced by iTBS correlated with the functional reorganization of the primary motor cortices in patients experiencing lower limb spasticity. Participants were randomly assigned to receive either real iTBS or sham iTBS during the first half of a 5-week indoor rehabilitation program. The results indicated that improvement in spasticity was more pronounced in the iTBS group compared to the sham iTBS group at the end of the stimulation session (VAS, p=0.026). While MAS scores improved in both groups, there was no significant difference between them. Furthermore, iTBS significantly affected the balance of connectivity degree between the stimulated and homologous primary motor cortex (p=0.005), and changes in inter-hemispheric balance were correlated with spasticity improvement (p=0.015). However, there was no effect of iTBS on the global topology of the brain network, indicating that iTBS over the primary motor cortex does not alter the overall organization of the brain network [39].

Nielsen et al. [57] in a double-blind, placebo-controlled study (n=38 participants) investigated the impact of rTMS on spasticity. Participants in the intervention group received one session of 16 stimuli at 25 Hz rTMS targeting the leg motor area, followed by one session of five-minute sessions (twice daily for seven consecutive days The treatment group showed a significant improvement in MAS scores compared to the control group at day one post-treatment, (MD=-3.3±4.7 vs. 0.7±2.5, p=0.003). Additionally, the stretch reflex threshold significantly increased in the treatment group compared to the control group (4.3±7.5 deg/s vs. -3.8±9.7 deg/s, p=0.001). Both groups reported significant improvements in self-assessed ease of daily activities (p<0.05 for both groups). At day 8, there was no statistically significant difference in spasticity scores or self-assessed ease of activities of daily living (ADLs) between the groups, but the stretch reflex threshold remained significantly improved in the treatment group (p=0.028). None of the scores showed statistically significant differences between the two groups on day 16 [57].

San et al. [60] (n=16 participants) investigated the impact of rTMS on spasticity in the adductor hip muscles. All participants (including rTMS and sham rTMS) received 10 stimulation sessions along with PT and a rehabilitation program. The results indicated statistically significant improvements in bilateral MAS scores over time in the rTMS group (p=0.005), but no significant changes in the control group (p>0.05). Additionally, significant improvements in spasm frequency were observed in the rTMS group at both 1 week and 1-month post-intervention (p<0.01), with no significant differences in the control group (p>0.05). Compared to the control group, the rTMS group showed significant improvements in several other outcomes [60].

A RCT (n=34 SPMS) compared the effects of two rTMS protocols- high-frequency (20 Hz) rTMS (HF-rTMS) and iTBS on spasticity levels and associated symptoms in patients with spastic paraparesis [52]. Participants were randomized into three groups: HF-rTMS, iTBS, or sham stimulation. Both HF-rTMS and iTBS groups showed significant reductions in muscle tone (MAS scores, p<0.001) post-treatment, whereas the sham group did not exhibit significant changes (p=0.44). The reduction in spasticity levels persisted at 2 weeks post-intervention in both the HF-rTMS and iTBS groups. However, at 12 weeks post-intervention, a significant reduction in SESS score was only observed in the iTBS group. Reductions in pain and fatigue were only observed in the HF-rTMS group [52].

Another RCT (n=17 RRMS) evaluated the clinical effect and neurophysiological changes produced by iTBS on lower extremity spasticity [41]. The authors reported that 2-weeks of iTBS on the motor cortex contralateral to the most affected leg did not produce any significant clinical effect on spasticity. However, a significant decrease in the H/M amplitude ratio was observed in the treatment group from baseline after the first, fifth, and tenth sessions (p<0.05 for all), This effect was maintained up to 1 week after the last stimulation session (p=0.047). There were no significant changes in the sham control group [41].

Vibration therapy

Three studies explored various approaches to vibration therapy, including WBV, segmental muscle vibration, and local vibration [24,38,58]. Schyns et al. [24] in an RCT (n=16 participants) assessed the effectiveness of a WBV program on tone, muscle force, sensation, and functional ability in MS patients. Participants in group 1 received four weeks of WBV plus exercise (3 times/week), followed by two weeks of no intervention, and then four weeks of exercise alone (3 times/week), and participants in group 2 underwent the two treatment interventions in the reverse order. Overall, the exercise program demonstrated positive effects on muscle force and well-being, but there was insufficient evidence to suggest that the addition of WBV provided further benefit. Following the combination of WBV and exercises, there was no significant difference in MAS scores in either group, however, both groups showed a significant reduc-

tion in muscle spasms (p=0.02) and pain (p=0.036). Some improvements in functional abilities, as measured by the 10-meter walk and TUG test were observed, but these changes were not statistically significant (p>0.05 for both) [24].

A single-blind RCT (n=42 SPMS) examined the efficacy of segmental muscle vibration and BoNT-A injection, either alone or in combination, in reducing spasticity [58]. Participants were randomly assigned to three parallel groups: the vibration therapy group (receiving 30 minutes of 120 Hz segmental muscle vibration over the rectus femoris and gastrocnemius medial and lateral, three times/week for four weeks), the BoNT plus vibration therapy group (receiving BoNT-A injections in the rectus femoris, gastrocnemius medial and lateral, and soleus, in addition to segmental muscle vibration), and the BoNT group (receiving BoNT injection alone). The results showed a significant reduction in spasticity in all groups over time (MAS scores, p<0.001). Interestingly, patients in the BoNT-only group showed a significant increase in knee and ankle spasticity at the 22-week follow-up compared to 10 weeks post-intervention (p<0.05). Further, there was a significant reduction in fatigue (FSS scores) at both 10 weeks and 22 weeks compared to baseline in the vibration group and the BoNT-injection only group (p=0.03 and 0.02, respectively), while no differences were detected in the BoNT plus vibration group [58].

Another RCT (n=33 pwMS) compared the effects of 50 Hz versus 100 Hz local vibration (applied for 5 minutes to the right and left medial gastrocnemius muscles) on spasticity, functional performance, and muscle architecture [38]. Participants were randomly assigned to three groups: 50 Hz or 100 Hz local vibration, and the control group (receiving PT only). All participants received one hour of PT per day (three days a week for eight weeks). The 50 Hz vibration group demonstrated statistically significant reductions in spasticity and increases in fascicle length (p<0.05 for both). There was a significant improvement in ankle joint position sense, single-leg stance time, and limits of stability/postural sway range in the mediolateral direction in both vibration therapy groups (p<0.05 for all). Anteroposterior limits of stability and postural sway showed significant improvement across all groups (all p<0.05). The 50 Hz group exhibited significant improvement in all walking parameters (velocity, step length, and base of support values), while the 100 Hz group showed improvements only in velocity and step length (all p<0.05). The control group demonstrated significant improvements only in single support and stance phase percentages of the gait cycle (both p<0.05). Between-group comparisons revealed a significant difference only in mediolateral limits of stability (p<0.05), with better scores observed for the 50 Hz group compared to the 100 Hz and exercise groups [38].

Educational/self-management programs

Educational and self-management programs, aiming to empower individuals with knowledge and skills to understand, cope with, and manage their spasticity-related symptoms, were evaluated in three studies [43,44,48]. Hugos et al. [48] (n=40 pwMS) investigated the efficacy of a four-week group-delivered self-management program, including stretching instruction and support, in reducing spasticity. The results demonstrated a significant reduction in spasticity post-intervention in the intervention group in spasticity (MSSS-88 total scores=-27.8 vs. -3.7, p<0.03), in pain and discomfort subscale (-3.9 vs. 0.3, p<0.02) and muscle spasms subscale (-5.0 vs. 0.5, p<0.03). Additionally, participants in the intervention group experienced significant improvements in fatigue (p=0.03), depression (p=0.004), physical function (p=0.002), and knowledge about spasticity based on a written test (p<0.04). However, there were no significant group differences in any of these measures (p>0.05 for all) [48].

Ehling et al. [43] (n=20 participants) assessed the effectiveness of an individualized training program in reducing spasticity. Initially, all participants were introduced to predefined exercises targeting spasticity during their inpatient rehabilitation program, then were randomly assigned to either an APP-based home therapy program "MS-spasticity APP" (which included 85 exercises focusing on movement, strengthening and coordination of lower limbs and trunk and a video sequence showing a PT performing the exercise) or a paper-based home therapy program for three months. After three months, all received MS spasticity-based program for another three months. Compared to participants conventional paper-based program, participants in APP-based home program showed a significant reduction in spasticity (NRS scores MD=1.2, p=0.09). At 24 weeks follow-up, "MS spasticity APP" was associated with a decrease in spasticity (NRS scores MD=2.5±1.7) in all participants [43].

Another RCT (n=94 participants) conducted by the same group investigated the effects of multidisciplinary inpatient rehabilitation (MD) and an individualized self-training program delivered through a mobile APP on moderate to severe lower limb spasticity [44]. Following inpatient MD rehabilitation, those showing clinically relevant improvement in spasticity (≥20% on NRS) were randomly assigned in a 1:1 ratio to either the MS-Spasticity APP or a paper-based self-training program

for 12 weeks. Overall, the findings indicated a significant reduction in spasticity after inpatient MD rehabilitation (p<0.001), improvement in strength of lower extremities (p<0.001), and mobility outcome (p<0.001). Self-training program with the MS-Spasticity APP post-MD rehabilitation program showed sustained positive effects on spasticity, whereas paper-based self-training resulted in a worsening of spasticity (median NRS difference=1.0, 95% CI=1.7 to 0.3, p=0.009). Additionally, the MS-Spasticity APP was linked to significantly better adherence to self-training (95% vs. 72% completion rate, p<0.001) [44].

tDCS

Two studies evaluated the effectiveness of tDCS, a neuromodulation technique involving the APP of a low direct current to the scalp to modulate neuronal activity in the brain, for managing spasticity [45,50]. A single-center, randomized, double-blind, sham-controlled study (n=20 RRMS) investigated the efficacy of anodal tDCS compared to sham tDCS in modulating lower limb spasticity [50]. The intervention group received anodal tDCS stimulation to the primary motor cortex of the more affected side (20 minutes/day over 5 consecutive days). The findings showed no significant improvement in spasticity outcomes in both groups post-intervention (tDCS group: MAS and MSSS-88 scores, p>0.05). Further, there was no significant change in walking abilities in either group (MS Walking Scale, p>0.05 for both) [50].

A parallel arm RCT (n=20 RRMS) examined the effectiveness of anodal tDCS on spasticity [45]. The intervention group received active anodal tDCS targeting the ipsilesional motor cortex, with five consecutive daily sessions lasting 20 minutes each, while the control group received sham stimulation. There was no significant difference between the two groups in MAS scores post-treatment (p=0.22). However, compared to the sham group, the intervention group demonstrated significant improvement in the H/M amplitude ratio (MD=-0.16 vs. 0.07, p<0.05) and significant stability in H latency (MD=-0.54 vs. -1.03, p>0.05) [45].

PEMF devices

The effectiveness of electromagnetic therapy (pulsed electromagnetic therapy [53]; and magnetic pulsing device [Enermed] [59]) was evaluated in two studies. A multi-site, double-blind, placebo-controlled, cross-over trial (n=117 participants) assessed the effects of a pulsed electromagnetic therapy on MS-related spasticity, fatigue, bladder control, and QoL [53]. Participants received four weeks of the active and placebo treatments separated by a two-week washout period. The muscle spasm/spasticity measured at the end of each session showed statistically significant differences in favour of the active device group (p=0.04), while daily diary ratings showed no significant difference in treatment effects. The QoL index (QLI) (created using fatigue, pain, and spasticity scales) showed moderate inter-correlations (r=0.32 to 0.60). Compared to the control group, participants in the active device group showed significant improvement in fatigue (p=0.04) and QoL (p=0.03), but no significant differences in bladder control (p=0.26) or disability composite (p=0.77) [53].

Another double-blind trial (n=30 participants) evaluated the clinical and subclinical effects of a magnetic pulsing device (frequency range of 4–13 Hz) on disease activity [59]. The treatment group showed a significant improvement in the performance scale (PS) combined rating for bladder control, cognitive function, fatigue level, mobility, spasticity, and vision compared to the control group (-3.83±1.08 versus -0.17±1.07, change in PS, p<0.005). Additionally, there was a significant change in alpha electroencephalography magnitude during a language task between pre-treatment and post-treatment [59].

TENS

Two studies evaluated the impact of TENS [22,61]. A single-blind, cross-over trial (n=32 participants) randomly allocated participants into two groups: 60-minutes or 8 hours of daily TENS APPs (frequency of 100 Hz and pulse width of 0.125 ms) for 2 weeks, followed by a washout period of 2 weeks [22]. The results indicated no statistically significant differences in the Global Spasticity Score following either 60 minutes or eight hours of daily TENS (p=0.433 and 0.217, respectively). However, compared to the shorter 60-minute APP, the longer 8-hour APP duration resulted in a significant reduction in muscle spasms (p=0.038) and pain (p=0.008). At the end of the study (8–20 months), overall patients reported a reduction in symptoms: 87.5% for spasms, 73.3% for pain & 73.3% for stiffness [22].

Shaygannejad et al. [61] conducted a comparative study (n=52 participants) to assess the effectiveness of baclofen versus self-applied TENS for treating lower limb spasticity. Participants were randomly assigned to undergo a four-week treatment regimen either with baclofen (starting at 10 mg twice daily and increasing to 25 mg over three weeks) or self-applied TENS. MAS scores decreased from 1.77±0.29 at baseline to 0.73±0.70

(p<0.001) in the TENS group and from 1.73±0.38 to 1.15±0.63 in the baclofen group (p<0.001). Furthermore, the MAS score at the four-week follow-up was significantly lower in the TENS group compared to the baclofen group (MD=-0.42, 95% CI=-0.79 to -0.05, p<0.05) [61].

Shockwave therapy

A double-blind, randomized, placebo-controlled study (n=78 pwMS) evaluated the effectiveness of radial shock wave therapy (RSWT) (one session/week for 4 weeks) targeting the ankle extensor muscles for painful hypertonia [54]. Following RSWT, muscle tone significantly decreased one week after the final session (MD in MAS score: -0.78, p<0.0001). Pain levels decreased across all follow-up evaluations (one week after the initial session, and one week and four weeks after the last session, p<0.001 for all), while spinal excitability (H-reflex) and walking parameters remained unaffected. There were no significant changes in any parameters observed after the placebo treatment [54].

CAM-acupuncture

A crossover RCT (n=12 participants) evaluated the efficacy of acupuncture in alleviating symptoms related to spasticity [44]. Participants were randomly assigned to receive either acupuncture treatment (twice weekly for 4 weeks) or no treatment (control). This was followed by a 4-week washout period, after which participants switched to the alternative condition for another 4 weeks. Following the treatment period, a notable improvement in spasticity was observed in the treatment group, specifically in the right hip flexors (MAS score, p=0.030). There were no significant changes observed in any other lower limb muscles (p>0.05 for all). Further, there were no statistically significant improvements noted in gait or balance measures [44].

Quality of evidence

The GRADE approach was utilized to synthesize and interpret the quality of evidence from the included studies [33,35]. According to this method, all RCTs were initially assigned a "high (+4)" rating as the default for study design. This rating was subsequently downgraded based on the presence of factors within five domains: risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias. Majority of the studies were downgraded based on the methodological quality (risk of bias), followed by imprecision and indirectness (small sample size, indirect comparisons, lack of convenient control groups). Detailed GRADE assessments are presented in Table 2, and an overall summary of findings is summarised below.

Summary of key findings

The overall evidence supporting the beneficial effect of different non-pharmacological interventions in mitigating spasticity in pwMS is summarised below:

Physical therapeutic programs

In total, 12 studies (n=737 participants) evaluated the impact of different types of physical activity programs, either independently or in conjunction with other interventions. The findings suggest that there are:

- Moderate certainty evidence for PT programs compared to usual care or no intervention in short-term
- Low-certainty evidence for physical activity program compared to other non-pharmacological interventions for short-term
- Low certainty evidence for the addition of active physiotherapy after BoNT injection in reducing spasticity for short-term
- Very low certainty evidence for physical activity programs compared to other non-pharmacological interventions for longer-term

There is also some evidence for the beneficial impact of physical activity programs on walking, balance, fatigue and QoL.

rTMS

Six studies (n=142 participants) evaluated the different forms of rTMS. The findings suggest the following evidence supporting the beneficial effect of rTMS on the reduction of spasticity:

- Moderate certainty evidence for short-term benefits of rTMS compared to sham stimulation for improved spasticity, functional abilities and stretch reflex thresholds;
- Low certainty evidence for short-term benefits of rTMS in combination with rehabilitation program for improved spasticity and functional and abilities;
- Low certainty evidence for iTBS as a single intervention or in combination with exercise therapy reduced spasticity after two weeks of treatment

There is also some evidence for the beneficial impact of rTMS on ADLs, reduction of spasticity-related spinal hyper-excitability (H-reflex amplitude), pain, fatigue and QoL.

Table 2. Levels of quality of evidence (GRADE approach[a])

Reference	Bias risk	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE
Abadi Marand et al., 2023 [36]	+ (-1)	NS	NS	+ (-1)	U	Low (+2)
Andreu-Caravaca et al., 2022 [37]	+ (-1)	NS	-1	NS	U	Low (+2)
Ayvat et al., 2021 [38]	++ (-2)	NS	NS	+ (-1)	U	Very low (+1)
Boutière et al., 2017 [39]	++ (-2)	NS	-1	NS	U	Very low (+1)
Calabrò et al., 2017 [40]	+ (-1)	NS	NS	+ (-1)	U	Low (+2)
Dieguez-Varela et al., 2019 [41]	+ (-1)	NS	-1	NS	U	Low (+2)
Eftekharsadat et al., 2015 [42]	++ (-2)	NS	NS	NS	U	Low (+2)
Ehling et al., 2017 [43]	++ (-2)	NS	-1	NS	U	Very low (+1)
Ehling et al., 2022 [44]	++ (-2)	NS	NS	+ (-1)	U	Very low (+1)
El Habashy et al., 2022 [45]	++ (-2)	NS	-1	NS	U	Very low (+1)
Ergül et al., 2021 [46]	+ (-1)	NS	NS	+ (-1)	U	Low (+2)
Giovannelli et al., 2007 [47]	++ (-2)	NS	NS	NS	U	Low (+2)
Hugos et al., 2017 [48]	++ (-2)	NS	NS	+ (-1)	U	Very low (+1)
Hugos et al., 2024 [49]	++ (-2)	NS	NS	NS	U	Low (+2)
Iodice et al., 2015 [50]	++ (-2)	NS	-1	NS	U	Very low (+1)
Karpatkin et al., 2023 [51]	++ (-2)	NS	-1	NS	U	Very low (+1)
Korzhova et al., 2019 [52]	+1 (-1)	NS	NS	NS	U	Moderate (+3)
Lappin et al., 2003 [53]	+ (-1)	-1	NS	+ (-1)	U	Very low (+1)
Marinelli et al., 2015 [54]	+ (-1)	-1	NS	+ (-1)	U	Very low (+1)
Miller et al., 2007 [22]	++ (-2)	-1	NS	NS	U	Very low (+1)
Mori et al., 2011 [55]	+ (-1)	NS	-1	NS	U	Low (+2)
Negahban et al., 2013 [56]	+ (-1)	NS	NS	NS	U	Moderate (+3)
Nielsen et al., 1996 [57]	+ (-1)	-1	NS	NS	U	Low (+2)
Paoloni et al., 2013 [58]	+ (-1)	-1	NS	+ (-1)	U	Very low (+1)
Richards et al., 1997 [59]	+ (-1)	-1	-1	+ (-1)	U	Very low (0)
Şan et al., 2019 [60]	++ (-2)	NS	NS	NS	U	Low (+2)
Schyns et al., 2009 [24]	++ (-2)	NS	-1	NS	U	Very low (+1)
Shaygannejad et al., 2013 [61]	++ (-2)	-1	NS	+ (-1)	U	Very low (0)
Tarakci et al., 2013 [62]	+ (-1)	NS	NS	NS	U	Moderate (+3)
Velikonja et al., 2010 [63]	++ (-2)	-1	-1	NS	U	Very low (0)
Vermöhlen et al., 2018 [64]	++ (-2)	-1	NS	NS	U	Very low (+1)
Zrzavy et al., 2021 [65]	++ (-2)	NS	NS	NS	U	Low (+2)

+, serious; ++, very serious; NS, not serious; U, undetected.
[a]GRADE: Grading of Recommendations Assessment, Development and Evaluation. The judgment of value given for each study is specifically based on the data related to this review.

Vibration therapy

Three studies (n=97 participants) explored various approaches to vibration therapy, including WBV, segmental muscle vibration, and local vibration. The findings suggest:

- Very low certainty evidence for the beneficial effect of WBV with or without exercise program in reducing spasticity
- Very low certainty evidence for the beneficial effect of local vibration with or without exercise program in reducing spasticity
- Very low certainty evidence for the beneficial effect of segmental muscle vibration with or without BoNT injections in reducing spasticity

Self-management educational program

Three studies (n=154 participants) evaluated various forms of educational self-management programs, which included approaches such as group self-management programs and electronic app-based self-management exercise programs, the findings from these studies suggest:

- Very low certainty evidence for the beneficial effects of software-based self-management programs compared to paper-based programs for spasticity
- Very low certainty evidence for the beneficial effects of self-management programs compared to usual care for spasticity

There is also some evidence beneficial impact of educational.

tDCS

Two studies (n=40 participants) evaluated the different forms of tDCS and found:

- Very-low certainty evidence for tDCS compared to sham in reducing spasticity

TENS

Two studies (n=84 participants) evaluated the impact of TENS and found:

- Very low certainty evidence for the beneficial effect of different intensities of TENS in reducing spasticity
- Very low certainty evidence for the beneficial effect of TENS with or without Baclofen in reducing spasticity

There is also some evidence for the beneficial effect of TMS on muscle spasms and pain.

Pulsed electromagnetic therapy

Two studies (n=147 participants) investigated the effectiveness of Pulsed Electromagnetic therapy (Enermed) and found:

- Very low certainty evidence for the short-term beneficial effects of pulsing magnetic fields for spasticity, bladder control, cognitive function, fatigue level, mobility, and vision

Radial shockwave therapy

One study (n=68 participants) assessed the effectiveness of shock wave therapy over ankle extensor muscles and revealed:

- Very low certainty evidence for the short-term beneficial effects of pulsing magnetic fields for spasticity, reducing pain, or enhancing spinal excitability programs on improving ADLs, fatigue, and condition-specific knowledge and compliance.

Acupuncture

The efficacy of acupuncture was assessed in one study (n=12 participants), which suggests:

- Very low certainty evidence for the beneficial effects of acupuncture in alleviating spasticity-related symptoms

There was no effect of acupuncture on muscle strength, gait, and balance.

Non-pharmacological interventions for managing spasticity in MS are generally considered safe and well-tolerated [12,20,66]. Despite some included studies did not assess the adverse effects profile, reported adverse events and withdrawals were minor and infrequent. The overall findings suggest that physical therapeutic interventions were associated with a low risk of adverse effects, especially when tailored to the patient's individual needs and conducted under professional supervision. These interventions were well-tolerated by patients, with few reports of adverse events such as muscle soreness or fatigue [20,67]. Notably, interventions such as rTMS, tDSC, vibration therapy, or shock wave therapy interventions did not result in reported adverse effects. It is recommended that the severity of spasticity, and the patient's overall health, need to be considered with the proper execution of the techniques from trained professionals to avoid potential injuries or exacerbation of symptoms [66,67]. Further, the long-term safety of these interventions needs to be explored.

DISCUSSION

Addressing spasticity in MS remains a significant challenge due to its complex nature, the varying efficacy and safety profiles of available interventions, and the variability and reliability of spasticity assessment tools [13,68,69]. Non-pharmacological interventions play a role as primary and/or adjunctive therapies for addressing spasticity-related issues. This review rigorously assesses evidence from published RCTs to determine the efficacy of non-pharmacological interventions in managing spasticity amongst pwMS. A total of 32 RCTs investigated a range of non-pharmacological interventions (including physical therapies, electromagnetic therapy, electrical nerve stimulation, vibration therapy, shock wave therapy, educational/self-management programs, and CAM). The most frequently examined intervention was a physical therapeutic program followed by rTMS. The included trials exhibited considerable heterogeneity in terms of intervention types (contents, intensity/duration), delivery settings (institution, community, home), outcome measures used, and study quality. Further, variations were noted in comparison (control) groups employed and assessment periods across the trials. As a result, quantitative synthesis was deemed impractical, and a qualitative synthesis based on the 'best evidence' was provided. The findings indicate that the current evidence supporting the efficacy of non-pharmacological interventions for spasticity management in pwMS is still relatively weak. The quality of evidence for most outcomes is of 'low' or 'very low' quality primarily due to the risk of bias and imprecise and inconsistency of results across the small number of included studies.

The findings reflect the growing acceptance of various non-pharmacological interventions in recent years. All studies in-

cluded appropriate populations (adult participants with MS), but only 19 trials reported using commonly accepted clinical criteria (such as those by McDonald, Poser, or Pollman). Many interventions, notably exercise interventions, lacked detailed descriptions necessary for replication. Additionally, there was considerable variation in stimulation protocols (frequency, total number of stimuli, stimulation intensity) among the included studies evaluating non-invasive brain/nerve stimulations. Comparisons with conventional groups (no treatment or placebo/sham) were lacking in over two-thirds of the trials, which predominantly compared active interventions against other non-pharmacological or pharmacological interventions. There are no 'gold standard' treatments for spasticity and the efficacy of many of the evaluated interventions is still unknown [12]. An accurate judgment of their effect is superlative that the intervention is compared to a conventional group (no treatment or placebo/sham). However, descriptions of control arms, particularly those using 'usual care' or 'sham/placebo,' were often inadequate in many included studies.

The methodological quality of the included trials was generally rated as 'low' due to significant flaws in the design, including high risks of bias related to randomization procedures, blinding, allocation concealment, and outcome analysis.

Furthermore, inadequate detail was provided to assess potential biases in certain methodological quality domains (Figs. 2, 3). Patient-related factors and therapy delivery details were not adequately addressed, impacting outcomes such as patient motivation and self-efficacy. The generalizability of results was limited, as many included studies were conducted in a single center and with strict inclusion/exclusion criteria, and insufficient data on longer-term follow-up.

Most outcome measures for spasticity used across the included studies were validated, with the most common being the MAS followed by the MSSS-28. However, there were concerns regarding the indirectness of certain outcome measures as some studies did not provide details on measurement tools used, including scoring and analysis procedures. Further, patient-reported scales [57,59] and modified MSQLI [53] were not validated and it was not clear if they captured the true values. There was also marked heterogeneity in assessment timepoints with most trials assessing the outcomes immediately following the interventions. Imprecision in effect estimates was noted, with a significant number of small studies (n=12 studies with <30 participants). Further, due to the limited number of studies evaluating specific interventions, the quality of evidence was judged based on a single or two trials. Adverse events were not frequently reported, and there was no information on the cost-benefit profiles of these strategies. Subgroup analysis based on the type of MS, disease severity (EDSS scores), disease duration, and affected site (upper limb, lower limb, or both) was not feasible due to insufficient data.

This review underscores existing gaps in the literature and highlights the efficacy of certain non-pharmacological interventions for MS spasticity. There are several published systematic reviews assessing specific non-pharmacological interventions for spasticity management in individuals with MS. The overall findings and conclusions of this review align with those of these published reviews in this domain. Etoom et al. [20] in a meta-analysis (n=29 studies) examined the effectiveness of various types of physiotherapy interventions including exercise therapy, electrical stimulation, RSWT, vibration, and standing, on spasticity in pwMS. The authors did not limit their inclusion criteria solely to RCTs and included other study types such as clinical-controlled and pre-post design studies. The findings suggest that PT interventions can be a safe and beneficial option for spasticity in pwMS, however, the authors could not draw firm conclusions as the included articles were heterogeneous and lacked adequate reporting of interventions and patient characteristics [20].

Another systematic review [70] investigated the effectiveness of both pharmacological and non-pharmacological interventions targeting spasticity on functional clinical outcomes in pwMS. The authors included 8 articles examining the effect of different non-pharmacological interventions and reported limited evidence for the beneficial effects of non-pharmacological interventions targeting spasticity [70]. This was consistent with the findings of our review. The efficacy of rTMS was evaluated in several systematic reviews [21,27,71]. Consistent with our findings, these published reports also found apparent discrepancies in the results in this area and many using rTMS as an adjunct therapy with other rehabilitation programs. Another systematic review examined the effects of TENS for the management of spasticity in different neurological conditions, including MS [23]. Similar to our findings, the authors concluded that evidence for the use of TENS for the management of spasticity in MS is still limited and can be used as an adjunct therapy [23].

One of the main issues in managing spasticity is the variability and reliability of assessment tools. Despite the availability of various assessment tools, none have proven to be consistently

reliable in clinical and research settings [68,69]. The MAS is the most widely used clinical measure, assesses resistance during passive muscle stretching and scores it on a 6-point ordinal scale. It has been criticized for its subjective nature and poor inter-rater reliability resulting in substantial variability in MAS scores [72]. Studies have shown that the MAS may not accurately reflect the severity of spasticity due to its simplistic ordinal scale, which does not capture the dynamic aspects of muscle resistance and can affect the accuracy and consistency of spasticity measurement [4,68,72]. Similarly, the MSSS-88, designed to assess the impact of spasticity on daily activities, has faced challenges related to its sensitivity and specificity. While it provides a more comprehensive view by including patient-reported outcomes, it is still subject to variability in patient perception and reporting, which can lead to inconsistencies in the assessment of spasticity severity and its impact on daily life [69]. Further, other neurophysiological approaches, such as H-reflex and EMG, by assessing the electrical activity of muscles and the excitability of spinal reflex pathways, offer more objective and quantifiable measurements of spasticity [73]. However, these techniques necessitate specialized equipment, advanced technology and skilled personnel to administer and interpret the results accurately, limiting their widespread adoption in clinical practice [73,74]. The variability in how these tools are administered and interpreted further complicates their reliability [69]. These limitations underscore the need for developing more reliable, valid, and standardized tools to evaluate spasticity, ensuring improved accuracy of diagnosis and severity, the effectiveness of interventions, and better clinical outcomes.

Study limitations

This review has several limitations. First, selection bias in the literature search cannot be entirely ruled out, as the search strategy primarily focused on cited literature despite using a broad range of terms to capture the widest possible selection of relevant literature. Additionally, studies where spasticity was incidentally measured (i.e., primary goal of the study was not to evaluate the reduction of spasticity), may have been overlooked or underreported. However, the literature search employed was comprehensive, utilizing a multi-pronged approach that included health science databases, trial registries, and grey literature. Study selection, data extraction, and quality assessment were conducted by two or more authors to ensure reliability. It is also important to note that this review did not evaluate pharmacological or surgical approaches, as these were beyond its scope. Publication bias remains a concern, as negative trials may remain unpublished [75]. Reference bias [76] is another potential confounder, as the search strategy included examining reference lists within relevant papers for additional articles that might have been missed in electronic searches. Given these limitations, the quality of evidence and the external validity of findings should be interpreted with caution. This is consistent with published guidelines and reviews on spasticity management [13,25,70,77]. Readers are encouraged to contact the authors regarding any high-quality studies meeting the review criteria that have not yet been included.

CONCLUSION

Recent advancements in spasticity management show evidence of the effectiveness of exercise programs in reducing spasticity and enhancing functional outcomes. However, while non-invasive brain stimulation techniques like rTMS or iTBS show potential as interventions in managing spasticity in pwMS, however, current evidence is insufficient to recommend their routine use. Currently, there is no supporting evidence for other non-pharmacological interventions in managing MS-related spasticity.

The review highlights the need for a multimodal approach involving an interdisciplinary team with regular follow-up, individualized care based on 'needs', and factors such as disease duration, spasticity characteristics, functional impairment, cost, patient/caregiver preferences. Accurate assessment, measurement, and clinician involvement in building evidence through practice is essential. This review emphasizes the variability in the effectiveness of non-pharmacological interventions due to therapist and operator dependency and potential multiple combined mechanisms (known and unknown) or 'bundled effects' [78]. The findings and clinical relevance of this review should be validated with future well-designed trials with larger sample sizes and longer-term follow-ups to improve the effective management of spasticity in MS.

CONFLICTS OF INTEREST

The review authors are professionals in the field of Physical and Rehabilitation Medicine who wish to provide the best possible service to their patients. No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

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SUPPLEMENTARY MATERIALS

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Appendix 1. Search strategies

MEDLINE

1. exp Muscle Spasticity/
2. exp Muscle Weakness
3. exp Muscle Hypertonia/
4. ("spasm*" or "muscle spasticity" or "spasticity" or "muscular spasm*" or "spastic" or "spastic paretic syndrome" or "spasticism" or "hypertonia").mp
5. 1 or 2 or 3 or 4
6. exp Multiple Sclerosis/
7. (demyelinating disease or demyelinating diseases or demyelinating disorder or demyelinating disorders).mp
8. exp Optic Neuritis/
9. (Multiple Sclerosis or Encephalomyelitis, Autoimmune, Experimental or Neuromyelitis Optica or Demyelinating Diseases).mp
10. *Myelitis, Transverse/
11. "clinically isolated syndrome".mp
12. (devic disease or Devic Syndrome or Devic's syndrome).mp.
13. transverse myelopathy.mp
14. disseminated sclerosis.mp
15. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 5 and 15
17. randomized controlled trial.pt
18. controlled clinical trial.pt
19. randomized.ab
20. placebo.ab
21. randomly.ab
22. trial.ab
23. groups.ab
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 16 and 24
26. exp animals/ not humans.sh
27. 25 not 26
28. exp Rehabilitation/
29. exp Neurological Rehabilitation/
30. exp Rehabilitation Centers/
31. exp Rehabilitation, Vocational/
32. exp Hospitals, Rehabilitation/
33. exp Physical Therapy Modalities/
34. exp Exercise/ or exp Exercise Therapy/
35. exp Occupational Therapy/
36. exp Transcutaneous Electric Nerve Stimulation/
37. exp Extracorporeal Shockwave Therapy/
38. (repetitive transcranial magnetic stimulation or rTMS).mp
39. exp Vibration/
40. (vibration or whole body vibration or WBV).mp
41. exp Transcranial Magnetic Stimulation/
42. (Intermittent Theta Burst Stimulation or iTBS).mp
43. exp Transcutaneous Electric Nerve Stimulation/
44. exp Self Care/
45. (Patient Education Handout or Education or Health Education).mp
46. (physical and rehabilitation).mp
47. exp "Physical and Rehabilitation Medicine"/
48. (pulsed electromagnetic therapy or magnetic pulsing device).mp
49. Self-Help Devices.mp
50. (assistive device* or assistive technolog*).mp
51. (orthotic * or orthotic devices).mp
52. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 25 and 52

Cochrane CENTRAL

#1. MeSH descriptor: [Multiple Sclerosis, Chronic Progressive] explode all trees
#2. MeSH descriptor: [Multiple Sclerosis, Relapsing-Remitting] explode all trees
#3. (multiple sclerosis):ti,ab,kw
#4. MeSH descriptor: [Optic Neuritis] explode all trees
#5. MeSH descriptor: [Demyelinating Diseases] this term only
#6. MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only
#7. MeSH descriptor: [Myelitis, Transverse] explode all trees
#8. ("Transverse Myelopathy"):ti,ab,kw
#9. MeSH descriptor: [Encephalomyelitis, Acute Disseminated] explode all trees
#10. (neuromyelitis optica):ti,ab,kw OR (NMO spectrum disorder):ti,ab,kw
#11. (optic neuritis):ti,ab,kw
#12. (demyelinating disease):ti,ab,kw OR (Demyelinating Autoimmune):ti,ab,kw
#13. (clinically isolated syndrome):ti,ab,kw
#14. (transverse myelitis):ti,ab,kw
#15. (encephalomyelitis):ti,ab,kw
#16. ("encephalomyelitis"):ti,ab,kw OR ("encephalo-myelitis"):ti,ab,kw
#17. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR#15 OR #16
#18. MeSH descriptor: [Occupational Therapy] explode all trees
#19. MeSH descriptor: [Rehabilitation] explode all trees
#20. (Rehabilitat*):ti,ab,kw
#21. MeSH descriptor: [Exercise] explode all trees
#22. (Exercise):ti,ab,kw
#23. MeSH descriptor: [Physical Therapy Modalities] explode all trees
#24. MeSH descriptor: [Exercise Movement Techniques] explode all trees
#25. MeSH descriptor: [Exercise Therapy] explode all trees
#26. (Exercise Therap*):ti,ab,kw
#27. MeSH descriptor: [Physical Fitness] explode all trees
#28. MeSH descriptor: [Physical and Rehabilitation Medicine] explode all trees
#29. MeSH descriptor: [Endurance Training] explode all trees
#30. MeSH descriptor: [Resistance Training] explode all trees
#31. MeSH descriptor: [Muscle Stretching Exercises] explode all trees
#32. (strengthening exercises):ti,ab,kw OR (stretching):ti,ab,kw
#33. (physical fitness):ti,ab,kw OR (physical rehabilitation):ti,ab,kw OR (physical endurance):ti,ab,kw OR (physical stimulation):ti,ab,kw OR (physical education):ti,ab,kw
#34. (resistance training):ti,ab,kw OR (strength training):ti,ab,kw OR (endurance program*):ti,ab,kw OR(resistance program*):ti,ab,kw AND (strength program*):ti,ab,kw
#35. (fitness program*):ti,ab,kw OR (aerobic training):ti,ab,kw OR (balance training):ti,ab,kw OR (gait training):ti,ab,kw
#36. (occupational therap*):ti,ab,kw
#37. MeSH descriptor: [Activities of Daily Living] explode all trees
#38. (Daily Living Activit*):ti,ab,kw OR (ADL):ti,ab,kw
#39. MeSH descriptor: [Self-Help Devices] explode all trees
#40. MeSH descriptor: [Splints] explode all trees
#41. MeSH descriptor: [Patient Education as Topic] explode all trees
#42. (patient education):ti,ab,kw
#43. MeSH descriptor: [Health Literacy] explode all trees
#44. (Health Literacy):ti,ab,kw
#45. MeSH descriptor: [Counseling] explode all trees
#46. (Counseling):ti,ab,kw OR (Counselling):ti,ab,kw
#47. MeSH descriptor: [Self Care] explode all trees
#48. (self-care):ti,ab,kw OR (self-efficacy):ti,ab,kw
#49. (assistive device*):ti,ab,kw OR (assistive technolog*):ti,ab,kw
#50. (energy conservation):ti,ab,kw OR (energy management):ti,ab,kw
#51. MeSH descriptor: [Electromyography] explode all trees
#52. (electromyography):ti,ab,kw OR (EMG):ti,ab,kw
#53. (transcutaneous electric nerve stimulation):ti,ab,kw OR (TENS):ti,ab,kw

#54. MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
#55. MeSH descriptor: [Ultrasonic Therapy] explode all trees
#56. (shock wave*):ti,ab,kw OR (therapeutic ultrasound):ti,ab,kw
#57. MeSH descriptor: [Ultrasonic Waves] explode all trees
#58. (Orthotic*):ti,ab,kw
#59. MeSH descriptor: [Orthotic Devices] explode all trees
#60. (repetitive transcranial magnetic stimulation):ti,ab,kw OR (rTMS):ti,ab,kw
#61. MeSH descriptor: [Transcranial Magnetic Stimulation] explode all trees
#62. (thermotherap*):ti,ab,kw
#63. MeSH descriptor: [Hyperthermia, Induced] explode all trees
#64. MeSH descriptor: [Acupuncture] explode all trees
#65. MeSH descriptor: [Acupuncture Therapy] explode all trees
#66. (hydrotherap*):ti,ab,kw
#67. MeSH descriptor: [Hydrotherapy] explode all trees
#68. (Biofeedback):ti,ab,kw
#69. MeSH descriptor: [Biofeedback, Psychology] explode all trees
#70. (vibratory stimulation):ti,ab,kw OR (wholebody vibration):ti,ab,kw
#71. MeSH descriptor: [Vibration] explode all trees
#72. (uni-disciplinary therap*):ti,ab,kw OR (unidisciplinary therap*):ti,ab,kw OR (physiotherap*):ti,ab,kw OR(neurodevelopmental treatment):ti,ab,kw OR (static positioning):ti,ab,kw
#73. (continuous passive motion robotics):ti,ab,kw
#74. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR#63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73
#75. MeSH descriptor: [Muscle Weakness] explode all trees
#76. MeSH descriptor: [Spasm] explode all trees
#77. MeSH descriptor: [Muscle Spasticity] explode all trees
#78. MeSH descriptor: [Muscle Hypertonia] explode all trees
#79. (spastic paretic syndrome):ti,ab,kw OR (spasticism):ti,ab,kw OR (hypertonia):ti,ab,kw
#80. (spasm*):ti,ab,kw OR (muscle spasticity):ti,ab,kw OR (spasticity):ti,ab,kw OR (muscular spasm):ti,ab,kwAND (spastic):ti,ab,kw
#81. #75 OR #76OR #77 OR #78 OR #79 OR #80
#82. #17 AND #74 AND #81

Embase

#1. 'multiple sclerosis'/exp
#2. 'multiple sclerosis':ab,ti
#3. 'demyelinating disease'/de
#4. 'optic neuritis'/exp
#5. 'acute disseminated encephalomyelitis'/exp
#6. 'transverse myelitis'/exp
#7. 'transverse myelitis':ab,ti OR 'transverse myelopathy':ab,ti
#8. 'neuromyelitis optica':ab,ti
#9. 'optic neuritis':ab,ti
#10. 'demyelinating disease':ab,ti OR 'demyelinating autoimmune':ab,ti
#11. 'demyelinating disorder':ab,ti
#12. 'clinically isolated syndrome':ab,ti
#13. encephalomyelitis:ab,ti OR 'encephalo-myelitis':ab,ti
#14. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15. 'rehabilitation'/exp
#16. rehabilitat*:ab,ti
#17. 'exercise'/exp
#18. exercise:ab,ti
#19. 'exercise therap*':ab,ti
#20. 'physiotherapy'/exp
#21. 'fitness'/exp

#22. 'rehabilitation medicine'/exp
#23. 'endurance'/exp
#24. 'physical stimulation'/exp
#25. 'convalescence'/exp
#26. 'endurance training'/exp
#27. 'resistance training'/exp
#28. 'stretching exercise'/exp
#29. 'physical fi tness':ab,ti OR 'occupational therapy':ab,ti OR 'physical rehabilitation':ab,ti OR 'physicalendurance':ab,ti OR 'physical stimulation':ab,ti OR 'physical education':ab,ti OR 'physical training':ab,ti OR'physical medicine':ab,ti OR 'physical therap*':ab,ti OR 'recovery of function':ab,ti OR 'endurance training':ab,ti OR'resistance training':ab,ti OR 'strength training':ab,ti OR 'endurance program*':ab,ti OR 'resistance program*':ab,ti OR 'strength program*':ab,ti OR 'fitness program*':ab,ti OR 'aerobic training':ab,ti OR 'balance training':ab,ti OR'gait traning':ab,ti
#30. 'transcutaneous electric nerve stimulation':ab,ti OR 'tens':ab,ti
#31. 'transcutaneous electric nerve stimulation'/exp
#32. 'ultrasound therapy'/exp
#33. 'shock waves':ab,ti OR 'therapeutic ultrasound':ab,ti
#34. 'ultrasonic waves'/exp
#35. 'orthosis':ab,ti
#36. 'orthotic devices'/exp
#37. 'repetitive transcranial magnetic stimulation':ab,ti OR 'rtms':ab,ti
#38. 'transcranial magnetic stimulation'/exp
#39. 'thermotherap*':ab,ti
#40. 'hyperthermia, induced'/exp
#41. 'occupational therapy'/exp
#42. 'occupational therap*':ab,ti
#43. 'daily life activity'/exp
#44. 'daily living activit*':ab,ti OR 'daily life activit*':ab,ti OR adl:ab,ti
#45. 'self help device'/exp
#46. 'self help device*':ab,ti OR 'self-help device*':ab,ti
#47. 'splint'/exp
#48. splint*:ab,ti
#49. 'patient education'/exp
#50. 'health literacy'/exp
#51. 'patient education':ab,ti OR 'health literacy':ab,ti
#52. 'counseling'/exp
#53. 'ergonomics'/exp
#54. ergonomic*:ab,ti OR 'ergo therap*':ab,ti
#55. 'kinesiotherapy'/exp
#56. 'self care'/exp
#57. 'self care':ab,ti OR 'self-effi cacy*':ab,ti OR 'self-care':ab,ti OR 'self effi cacy':ab,ti
#58. 'assistive technology'/exp
#59. 'assistive device*':ab,ti OR 'assistive technol*':ab,ti
#60. 'energy conservation'/exp
#61. 'energy conservation':ab,ti OR 'energy management':ab,ti
#62. 'acupuncture':ab,ti
#63. 'acupuncture therapy'/exp
#64. 'hydrotherap*':ab,ti
#65. 'hydrotherapy'/exp
#66. 'biofeedback':ab,ti
#67. 'biofeedback, psychology'/exp
#68. 'vibration'/exp
#69. 'vibratory stimulation':ab,ti OR 'wholebody vibration':ab,ti OR ‘WBV’
#70. 'uni-disciplinary therap*':ab,ti OR 'unidisciplinary therap*':ab,ti OR 'physiotherap*':ab,ti OR'neurodevelopmental treatment':ab,ti OR 'static positioning':ab,ti OR 'continuous passive motion robotics':ab,ti

#71. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR#57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70
#72. 'muscle weakness'/exp
#73. 'spasm'/exp
#74. 'muscle spasticity'/exp
#75. 'muscle hypertonia'/exp
#76. 'spasm*':ab,ti OR 'muscle spasticity':ab,ti OR 'spasticity':ab,ti OR 'muscular spasm*':ab,ti OR 'spastic':ab,tiOR 'spastic paretic syndrome':ab,ti OR 'spasticism':ab,ti OR 'hypertonia':ab,ti
#77. #72 OR #73 OR #74 OR #75 OR #76
#78. #14 OR #71 OR #77
#79. 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blindprocedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
#80. #78 AND #79
#81. 'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)
#82. #80 OR #81
#83. #80 NOT #81

CINHAL

S1. (MH "Multiple Sclerosis")
S2. TI "multiple sclerosis" OR AB "multiple sclerosis"
S3. (MH "Demyelinating Diseases")
S4. (MH "Optic Neuritis")
S5. TI "optic neuritis" OR AB "optic neuritis"
S6. (MH "Demyelinating Autoimmune Diseases, CNS")
S7. (MH "Encephalomyelitis, Acute Disseminated")
S8. (MH "Myelitis, Transverse")
S9. TI "neuromyelitis optica" OR AB "neuromyelitis optica"
S10. TI "demyelinating disease" OR AB "demyelinating disease" OR TI “Demyelinating Autoimmune” OR AB“Demyelinating Autoimmune”
S11. TI "demyelinating disorder" OR AB "demyelinating disorder"
S12. TI "clinically isolated syndrome" OR AB "clinically isolated syndrome"
S13. TI "transverse myelitis" OR AB "transverse myelitis" OR TI “Transverse Myelopathy” OR AB “Transverse Myelopathy”
S14. TI encephalomyelitis OR AB encephalomyelitis OR TI “encephalo-myelitis” OR AB “encephalo-myelitis”
S15. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16. (MH "Rehabilitation+")
S17. TI rehabilitat* OR AB rehabilitat*
S18. (MH "Exercise")
S19. TI Exercise OR AB Exercise
S20. (MH "Therapeutic Exercise+")
S21. TI exercise therap* OR AB exercise therap*
S22. (MH "Physical Therapy")
S23. (MH "Therapeutic Exercise")
S24. (MH "Physical Fitness")
S25. (MH "Physical Endurance")
S26. (MH "Physical Stimulation")
S27. (MH "Physical Education and Training")
S28. (MH "Endurance Training")
S29. (MH "Resistance Training")
S30. TI (“strengthening exercises” OR “stretching”) OR AB (“strengthening exercises” OR “stretching”)
S31. (MH “Stretching”)

S32. TI ((physical fitness OR physical rehabilitation OR physical endurance OR physical stimulation OR physical education OR physical training OR physical medicine OR physical therap* OR "recovery of function" OR endurance training OR resistance training OR strength training OR endurance program* ORresistance program* OR strength program* OR fitness program* OR aerobic training OR balance training OR gait training)) OR AB ((physical fitness OR occupational therapy OR physical rehabilitation OR physical endurance OR physical stimulation OR physical education OR physical training OR physical medicine OR physical therap* OR"recovery of function" OR endurance training OR resistance training OR strength training OR endurance program*OR resistance program* OR strength program* OR fitness program* OR aerobic training OR balance training OR gait training))
S33. TI Occupational Therap* OR AB Occupational Therap*
S34. TI ergotherap* OR AB ergotherap*
S35. (MH "Activities of Daily Living+")
S36. TI Daily Living activit* OR AB Daily Living activit*
S37. TI ADL OR AB ADL
S38. (MH "Assistive Technology Devices+")
S39. TI ("assistive device*" OR "assistive technolog*") OR AB ("assistive device*" OR "assistive technolog*")
S40. (MH "Splints+")
S41. TI splint* OR AB splint*
S42. (MH "Patient Education+")
S43. TI patient education OR AB patient education
S44. (MH "Health Literacy+")
S45. TI "Health Literacy" OR AB "Health Literacy"
S46. (MH "Counseling+")
S47. TI (counseling OR counselling) OR AB (counseling OR counselling)
S48. (MH "Ergonomics+")
S49. TI ergonomic* OR AB ergonomic* OR TI “ergo therap*” OR AB “ergo therap*”
S50. (MH "Self Care+")
S51. TI ("Self Care" OR "Self-Care") OR AB ("Self Care" OR "Self-Care") OR TI “self-efficacy*” OR AB “self-efficacy*”
S52. (MH "Energy Conservation")
S53. "Energy Conservation" OR AB "Energy Conservation" OR TI "Energy management" OR AB "Energy management"
S54. MH “Electromyography”)
S55. TI (“electromyography” OR “EMG”) OR AB (“electromyography” OR “EMG”)
S56. TI (“transcutaneous electric nerve stimulation” OR “TENS”) OR AB (“transcutaneous electric nerve stimulation” OR “TENS”)
S57. (MH “Transcutaneous Electric Nerve Stimulation”)
S58. (MH “Ultrasonic Therapy”)
S59. TI (“shock waves” OR “therapeutic ultrasound”) OR AB (“shock waves” OR “therapeutic ultrasound”)
S60. (MH “Ultrasonics”)
S61. TI “Orthotic*” OR AB “Orthotic*”
S62. (MH “Orthoses”)
S63. TI (“repetitive transcranial magnetic stimulation” OR “rTMS”) OR AB (“repetitive transcranial magneticstimulation” OR “rTMS”)
S64. (MH “Transcranial Magnetic Stimulation”)
S65. TI “thermotherap*” OR AB “thermotherap*”
S66. (MH “Hyperthermia, Induced”)
S67. TI “acupuncture” OR AB “acupuncture”
S68. (MH “Acupuncture”)
S69. TI “hydrotherap*” OR AB “hydrotherap*”
S70. (MH “Hydrotherapy”)
S71. TI “Biofeedback” OR AB “Biofeedback”
S72. (MH “Biofeedback, Psychology”)
S73. TI (“vibratory stimulation” OR “whole body vibration”) OR AB (“vibratory stimulation” OR “whole body vibration”)
S74. (MH “Vibration”)
S75. TI (“uni-disciplinary therap*” OR “unidisciplinary therap*” OR “physiotherap*” OR “neurodevelopmentaltreatment” OR “static positioning” OR “continuous passive motion robotics”) OR AB (“uni-disciplinary therap*” OR“unidisciplinary therap*” OR “physiotherap*” OR “neuro-developmental treatment” OR “static positioning” OR“continuous passive motion robotics”)
S76. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69OR S70 OR S71 OR S72 OR S73 OR S74 OR S75
S77. (MH “Muscle Weakness”)
S78. (MH “Spasm”)

S79. (MH "Muscle Spasticity")
S80. (MH "Muscle Hypertonia")
S81. TI ("spasm*" OR "muscle spasticity" OR "spasticity" OR "muscular spasm*" OR "spastic" OR "spasticparetic syndrome" OR "spasticism" OR "hypertonia") OR AB ("spasm*" OR "muscle spasticity" OR "spasticity"OR "muscular spasm*" OR "spastic" OR "spastic paretic syndrome" OR "spasticism" OR "hypertonia")
S82. S77 OR S78 OR S79 OR S80 OR S81
S83. S15 AND S76 AND S81
S84. S99. (MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pre-test-posttest design OR MH cluster sample OR TI (randomised OR randomized) OR AB(random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos)OR PT (randomized controlled trial) OR AB (CONTROL W5 GROUP) OR MH (CROSSOVER DESIGN) OR MH(COMPARATIVE STUDIES) OR AB (CLUSTER W3 RCT)) NOT ((MH ANIMALS+ NOT MH HUMAN) OR (MH(ANIMAL STUDIES) NOT MH (HUMAN)) OR (TI (ANIMAL MODEL) NOT MH (HUMAN)))
S85. S83 AND S84

Trial registry: 'clinicaltrials.gov'

Condition or disease:

"multiple sclerosis" OR "demyelinating diseases" OR "optic neuritis" OR "demyelinating autoimmune Diseases"

Impairment

"spasm*" OR "spasticity" OR "spastic" OR "spastic paretic syndrome" OR "spasticism" OR "hypertonia"

Intervention/treatment:

"uni-disciplinary therap*" OR "unidisciplinary therap*" OR "physiotherap*" OR "physical therap*" OR "recovery of function" OR "resistance training" OR "strengthtraining" OR "endurance program* OR "resistance program*" OR "strength program*" OR "fi tness program*" OR"aerobic training" OR "balance training" OR "physical training"OR "gait training" OR "movement" OR "rehabilitat*" OR "strengthening exercises" OR "stretching" OR "physical fitness" OR "neurodevelopmental treatment" OR "static positioning" OR "vibratory stimulation" OR "wholebody vibration" OR biofeedback OR hydrotherap* OR acupuncture OR thermotherap* OR "transcranial magneticstimulation" OR orthos* OR "shock waves" OR "therapeuticultrasound" OR "transcutaneous electric nerve stimulation" OR "electromyograph*" OR"occupational therap*" OR "physical stimulation" OR "physical education" OR "energy management" OR "energy conservation" OR "joint protection" OR "assistive device*" OR "assistive technolog*" OR "self care" OR "self-care" OR "self efficacy" OR "self-efficacy" OR ergonomic* OR "ergo therap*" OR counseling OR counselling OR "health literacy" OR "patient education" OR "splint*" OR "daily life activit*"

Trial registry: 'WHO-ICTRP' search strategy

("multiple sclerosis" OR "demyelinating diseases" OR "optic neuritis" OR "demyelinating autoimmune Diseases"OR "devic disease") AND ("spasm*" OR "muscle spasticity" OR "spasticity" OR"muscular spasm*" OR "spastic" OR "spastic paretic syndrome" OR "spasticism" OR "hypertonia") AND ("uni-disciplinary therap*" OR "unidisciplinary therap*" OR "physiotherap*" OR physical fitness OR physical rehabilitation OR physical endurance OR physical stimulation OR physical education OR physical training OR physical medicine OR physical therap* OR "recovery of function" OR endurance training OR resistance training OR strength training OR endurance program* OR resistance program* OR "strength program*" OR "fitness program*" OR "aerobic training" OR "neurodevelopmental treatment" OR "static positioning" OR occupational therapy OR "vibratory stimulation" OR "wholebody vibration"OR biofeedback OR hydrotherap* OR acupuncture OR thermotherap* OR "repetitive transcranialmagnetic stimulation" OR "rTMS" OR orthoses OR Orthotic* "strengthening exercises" OR "stretching" OR "shockwaves" OR "therapeutic ultrasound" OR "transcutaneous electric nerve stimulation" OR "TENS" OR"electromyography" OR "EMG")