Efficacy and Safety of Interventions for Cerebral Palsy: An Umbrella Review of 35 Meta-analyses

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Abstract: *Background;* At present, there is a shortage of strength and credibility of evidence regarding the efficacy and safety of intervention methods for individuals with cerebral palsy (CP).

Aim; To systematically evaluate the efficacy and safety of various intervention strategies for CP across physical, pharmacological, and biological domains through an umbrella review of meta-analyses.

Methods; PubMed, Web of Science, and Embase were systematically searched to identify peer-reviewed articles published prior to December 31, 2023. The study involved a meta-analysis of randomized controlled trials (RCTs) focusing on individuals diagnosed with CP who received interventions spanning physical (*e.g*., motor and stimulation therapies), pharmacological (*e.g*., botulinum toxin type A), and biological (*e.g*., stem cell therapy) domains. Two reviewers independently extracted data and assessed the quality of included studies using the AMSTAR tool. The GRADE system was used to evaluate the strength of evidence. The primary exclusion criteria were the absence of outcome measures related to efficacy and safety.

Results; This review encompasses 35 studies covering physical, biological, and pharmaceutical interventions, yielding a total of 31 outcome measures. The findings indicate that assistive technologies such as robot-assisted gait training, virtual-reality exercises, and hippotherapy, along with physical stimulation methods and stem cell therapy, positively influence multiple aspects of body functions and structures. Nevertheless, more comprehensive and stringent research is imperative to establish standardized therapeutic regimens. Type A botulinum toxin has proven effective in enhancing gait, albeit with safety concerns.

Conclusions; Our findings compared the effectiveness of multiple intervention methods for addressing various issues, yet further research is required to adopt more standardized approaches for evaluating the outcome measurements of these treatment plans. Future research should prioritize large-scale RCTs to validate these interventions and integrate multidisciplinary approaches to optimize functional outcomes in clinical practice.

Keywords: Cerebral palsy, Physical therapy, Pharmacotherapy, Biological intervention.

INTRODUCTION

Cerebral Palsy (CP), a group of disorders impairing movement and posture development, results from abnormal or impaired brain development, typically manifesting in infancy or early childhood [1-3]. With a multifaceted etiology involving prematurity, birth asphyxia, brain injuries, neonatal seizures, hypoglycemia, and infections [4], CP significantly impacts individuals' motor abilities, daily activities, and mobility. Clinically, it presents in various forms such as spastic, dyskinetic, ataxic, and mixed types [5], affecting diverse health aspects as defined by the International Classification of Functioning, Disability, and Health (ICF) [1]. The primary manifestations include muscle weakness, reduced range of motion, and spasticity [6, 7].

Globally, CP affects approximately 1 in 500 live births, with prevalence estimates ranging from 1.5 to 4 per 1,000 children, according to the World Health Organization (WHO) [8]. In high-income countries, the prevalence is reported at 2–3.5 per 1,000 children, while low-resource settings may exhibit higher rates due to limited access to perinatal care [9]. The condition not only imposes physical and psychological challenges on patients but also brings significant economic burdens on families and communities [10, 11]. This highlights the urgency for evidence-based public health interventions tailored to CP.

In managing CP's complex health challenges, various intervention strategies are employed, ranging from physical and pharmacological to biological

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interventions. While orthopedic surgeries and movement normalization once dominated CP treatment, recent trends favor intensive active training programs and device-assisted exercises [12]. However, the lack of standardized treatment protocols and the variability in defining intervention efficacy present challenges, particularly in ensuring the effectiveness and safety of these interventions [13]. In addition, heterogeneity in intervention types, doses, and outcome measures also poses significant challenges to evidence synthesis. Differences in study design, patient populations, and assessment tools often limit the comparability of results across trials, complicating the development of standardized treatment guidelines [14].

An umbrella review is a systematic synthesis of existing meta-analyses, designed to provide a high-level overview of the evidence while identifying consistencies, gaps, and methodological limitations across studies. Unlike traditional systematic reviews that analyze primary studies, an umbrella review evaluates pooled data from multiple meta-analyses, offering a broader perspective on the efficacy and safety of interventions [14, 15]. This approach is particularly valuable in CP research, where diverse interventions and heterogeneous outcomes complicate direct comparisons.

Therefore, this study aims to fill the gap in the existing literature by conducting an umbrella review of meta-analyses of randomized controlled trials (RCTs). The primary objective of our research is to assess the alleviation of disease-specific symptoms, which we consider a key indicator of intervention efficacy. Our secondary focus is on the safety of these interventions, particularly in terms of adverse effects occurring during the intervention process. By employing the ICF framework for systematic analysis, this review synthesizes high-level evidence to derive clinically meaningful conclusions. Ultimately, our findings aim to inform evidence-based clinical practice guidelines and optimize therapeutic strategies for individuals with CP.

METHODS

Search Strategy

We systematically searched PubMed, Web of Science, and Cochrane from their inception to December 31, 2023. The keywords utilized for the search were “cerebral palsy” and “meta-analysis” combined with intervention terms (*e.g.*, "physical therapy," "pharmacological," and "stem cell"). Two independent authors independently screened titles, abstracts, and full texts. Any discrepancies were resolved by a third author. This umbrella review was conducted in rigorous accordance with the PRISMA guidelines, and its protocol has been registered with PROSPERO (CRD42023480869).

Inclusion and Exclusion Criteria

Our inclusion criteria encompassed: 1) only meta-analyses containing ≥3 RCTs were included to ensure adequate data synthesis; 2) meta-analyses focusing exclusively on pediatric and adolescent CP patients were eligible; 3) All types of interventions aimed at patients with CP meet the eligibility criteria for inclusion; 4) only English-language publications were included. and 5) reporting on 31 predefined outcomes. Exclusion criteria included: 1) studies other than RCTs; 2) interventions targeting outcomes other than the predefined ones.

To address potential overlap of primary RCTs across included meta-analyses, we implemented a systematic approach: First, we created a comprehensive matrix mapping all primary RCTs to their source meta-analyses to identify studies included in multiple reviews. When encountering overlapping meta-analyses addressing the same intervention-outcome combination, we prioritized the most recent publication that demonstrated broader RCT coverage and higher methodological quality as assessed by AMSTAR criteria [15]. To ensure the robustness of our findings, we conducted sensitivity analyses for key outcomes by systematically excluding overlapping RCTs, which confirmed the consistency of our primary results.

Two reviewers independently verified compliance with these criteria, with disagreements resolved through discussion or third-party adjudication.

Included Interventions, and Comparisons

The finalized interventions meeting our criteria are categorized as physical, pharmacological and biological. Within physical interventions, we have subdivided these into motor and stimulation interventions.

Motor interventions encompass a wide array of techniques including action observation training, aerobic exercise, balance training, body weight supported treadmill training, casting, child-focused therapy, context-focused therapy, constraint-induced movement therapy, conventional physical therapy, external cues treadmill training, hand-arm bimanual intensive training (with and without lower extremity involvement), hippotherapy, muscle strength training, modified constraint-induced movement therapy, virtual reality (VR) training, overground gait training, respiratory exercises, robot-assisted gait training (RAGT), suit therapy, task-oriented training, and treadmill training.

Stimulation interventions comprise extracorporeal shockwave therapy, functional electrical stimulation, hyperbaric oxygen therapy, repetitive transcranial magnetic stimulation (rTMS), and whole-body vibration training.

Pharmacological interventions primarily involve the use of botulinum toxin type A (BoNT-A), while biological interventions are centered on stem cell therapy (SCT).

Control groups were divided into active and inactive controls. Active controls consisted of conventional treatments (CT) focusing on functionality improvement and rehabilitation techniques. Inactive controls included individuals on a waiting list (WL), receiving no treatment (NT), those given a placebo, and participants in sham control procedures.

Outcomes

The co-primary outcomes of this study focused on disease-specific primary symptom reduction, referred to as "efficacy," while the secondary outcome centered on safety, particularly adverse events occurring during the treatment process. Outcomes were framed within the ICF framework, which divides them into two main domains: body functions and structures, and activity or participation.

The domain of body functions and structures includes evaluations of arm, hand, and upper limb function; gross and fine motor functions; pulmonary function; gait improvements including gait velocity and step length; postural control; the 6-minute walk test (6WMT); ambulation; mobility; muscle strength, including grip strength; balance; dystonia; ankle and wrist range of motion (ROM); the timed up and go (TUG) test; and aspects of mental and psychological development such as developmental quotient, comprehension, and language expression, along with the recording of adverse events.

The domain of activity or participation encompasses assessments of participation, capacity, perceived and actual performance, and activities of daily living (ADL).

STATISTICAL ANALYSIS

To standardize the reporting of outcomes, we converted continuous non-standardized measures, such as weighted mean differences, to standardized mean differences (SMD). In situations where continuous outcome data was not available, odds ratios (ORs) were converted to SMD using R software (version 4.3.1).

In assessing gross motor function, we prioritized the gross motor function measure (GMFM). For fine motor function, emphasis was placed on the fine motor function measure (FMFM). In the evaluation of spasticity in dystonia, we relied on the Modified Ashworth Scale (MAS) score and the effective rate.

To ensure uniformity and enable direct comparisons, we standardized effect sizes as follows: an SMD greater than 0 indicates a beneficial effect for the intervention, whereas an SMD less than 0 indicates a beneficial effect for the control group. Cohen's conventions were employed to determine the magnitude of the effect size, with SMD values of 0.2, 0.5, and 0.8 indicating small, medium, and large effect sizes, respectively [16]. For the effective rate, an OR/RR greater than 1 favors the intervention. In the case of adverse events, an OR/RR less than 1 is indicative of a favorable outcome for the intervention.

Quality Assessment

The methodological quality of included meta-analyses was evaluated using the AMSTAR tool [17], which provides a comprehensive assessment of critical domains including protocol registration, literature search strategy, risk of bias evaluation, and appropriate statistical methods. The methodological quality is classified as low (<4), moderate (4-7), or high (>7) [18].

Credibility of Evidence

The credibility of evidence is evaluated using the grading of recommendations assessment, development, and evaluation (GRADE) system. The resulting GRADE evidence is categorized into four levels: high, medium, low, and very low.

RESULTS

Search Results

The initial search yielded 715 records. After eliminating duplicates and evaluating titles and abstracts, this number was reduced to 145. Ultimately, 35 meta-analyses met the inclusion criteria. The search process is depicted in Figure **1**.

Research Characteristics

Out of the 35 included meta-analyses, 30 focused on physical interventions, 3 on biological interventions, and 2 on pharmacological interventions. Among the physical interventions, motor interventions were the most extensively covered category, with 21 articles, followed by stimulation interventions, which had 9 articles.

Table **1** provides a comprehensive overview of the included meta-analyses. It presents key information such as intervention measures, types of controls, outcome indicators, the number of RCTs, participants involved, and the methodological quality assessed through the AMSTAR.

Quality and Credibility of Included Evidence

Among the 35 meta-analyses of RCTs, the median AMSTAR score was 7, with an interquartile range of 6-8. The overall quality score across all effect sizes was high for 14 MAs (34.15%), moderate for 26 (63.41%) and low for 1 (2.44%). These findings are summarized in Table **2**.

According to the GRADE system, a total of 116 pieces of evidence were reviewed. The credibility of the evidence was high for 12 meta-analyses (10.34%), moderate for 6 (5.17%), low for 40 (34.48%), and very low for 58 (50.00 %). These details can be found in Table **3**.

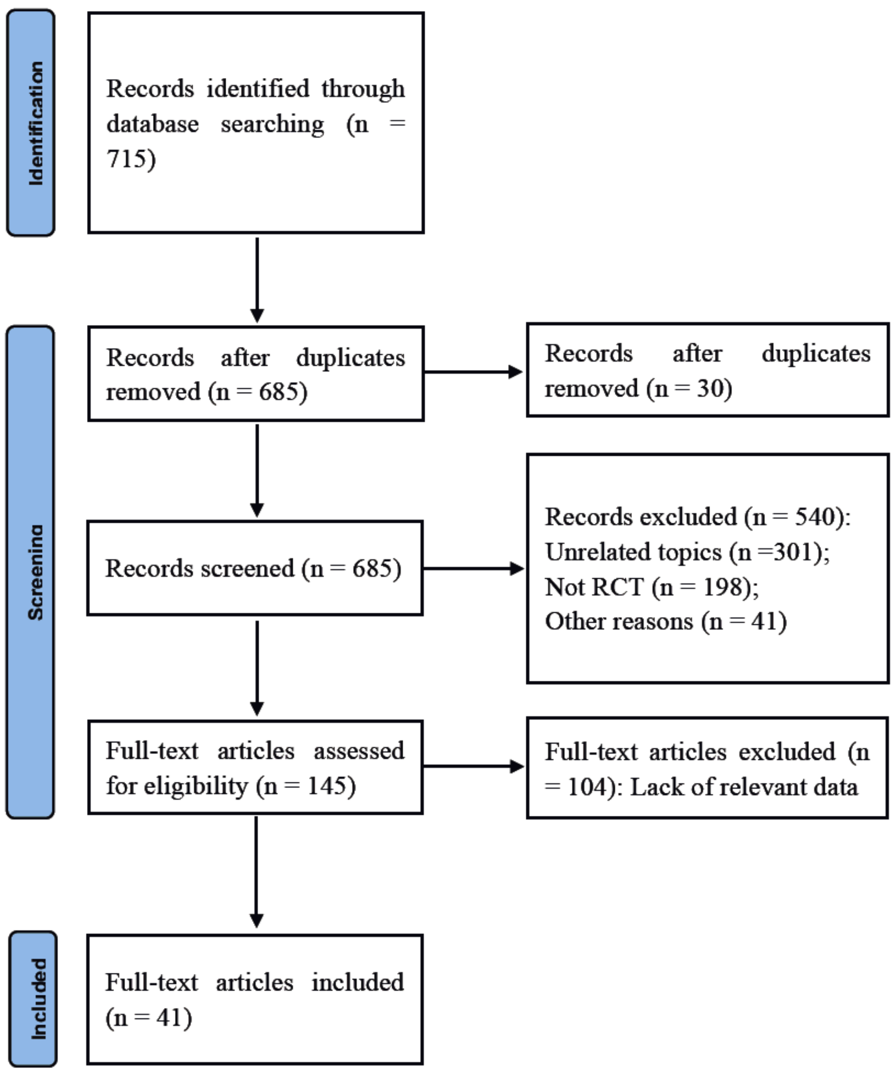

Figure 1: PRISMA flow chart.

Table 1: Meta-Analyses of Randomized Controlled Trials of Physical, Pharmacological, and Biological Interventions for Cerebral Palsy Included in the Umbrella Review

	Number of RCTs/ patients	Intervention	Controls	Outcomes	AMSTAR
Motor interventions					
Abdelhaleem[46]	6/307	AOT	PBO, WL/NT, CT	Capacity, perceived performance, actual performance	8
Araújo[47]	7/194	BTI + active interventions	Active interventions	Postural control	9
Conner[48]	8/188	RAGT	CT	GMF, gait velocity, 6WMT	8
De[49]	10/452	Hippotherapy	PBO, CT	GMF	7
De[50]	10/324	Respiratory exercises +RT	CT	Pulmonary function, GMF, 6WMT	8
Klaewkasikum[51]	15/716	Conservative treatment	CT	Gait improvements	8
Liang[52]	27/834	Exercise intervention	CT	GMF, gait velocity, muscle strength	6
Martins[53]	4/110	Suit therapy	Not reported	GMF	6
McLeod[54]	7/332	Active motor learning interventions	CT	GMF	6
Merino[55]	24/847	Muscle strength training	CT, NT	Balance, GMF, gait velocity, spasticity	7
Qian[56]	20/516	RAGT	RAGT	Gait velocity	7
Soares[3]	15/414	Aerobic exercise	CT	Aerobic capacity, GMF, mobility, participation, muscle strength, ADL	6
Wang[25]	14/470	RAGT	CT	GMF, balance, gait velocity, 6WMT, Dystonia	8
Yang[57]	22/788	Upper limb training	PBO	Functional improvement	7
Zai[29]	16/893	TOT	CT	GMF, balance, mobility	9
Chen[58]	19/504	VR	CT	Arm function, postural control, ambulation	4
Han[28]	11/442	VR	NT, CT	ADL	8
Hao[59]	18/643	VR	WL, CT	GMF, hand function, grip strength	7
Liu[60]	16/470	VR	CT	Balance	5
Liu[61]	16/513	VR	CT	Balance, GMF	7
Arpino[62]	4/223	Intensive physiotherapy	Non-intensive physiotherapy	GMF	4
Stimulation interventions					
cai[63]	13/451	WBV	CT	GMF, balance, TUG, 6WMT, ankle-ROM	6
chen[36]	14/421	NMES	CT	GMF, gait velocity	8
Kim[64]	5/104	ESWT	Not ESWT	Dystonia, ROM	4
Ou[65]	8/294	NMES	CT	Hand function, muscle strength, dystonia, wrist-ROM	6
Saquetto[66]	6/176	WBV	CT	GMF, gait velocity, muscle strength	6
Sun[67]	29/1653	rTMS	sham rTMS, CT	GMF, FMF, dystonia, comprehension, language expression	7
Zhang[23]	25/2146	HBOT	Not HBOT	GMF, developmental quotient, comprehension, language expression	8

Zhu[68]	9/282	FES	CT	Gait velocity, step length	7
Pulay[69]	16/414	WBV	Physiotherapy	Muscle strength, dystonia	8
Pharmacological interventions					
Albavera[19]	20/882	BoNT-A	PBO	Adverse events	4
Kumar[70]	5/190	BoNT-A	Casting	Spasticity	7
Biological interventions					
Eggenberger[22]	5/282	SCT	CT	Adverse events	6
Poh[21]	7/411	SCT	PBO, CT	GMF	3
Qu[20]	9/611	SCT	CT, regular medication	GMF	8

ADL - activities of daily living, AOT - action observation training, BoNT-A - botulinum toxin type-A, BTI - balance-training interventions CT - conventional treatment, FES - functional electrical stimulation, FMF - fine motor function, GMF - gross motor function, HBOT - hyperbaric oxygen therapy, NEMS - neuromuscular electrical stimulation, NT – not treatment, PBO – Placebo, RAGT - robotic assisted gait training, ROM - range of motion, rTMS - repetitive transcranial magnetic stimulation, SCT - stem cell therapy, TUG - timed up and go test, TOT - task-oriented training, VR - virtual reality train, WBV - whole body vibration train, WL – waiting list, 6WMT - six-minute walk test.

Table 2: Quality Appraisal Results of Included Systematic Reviews using the AMSTAR Tool

Study	**1. Was an 'a priori' design provided?**	**2. Was there duplicate study selection and data extraction?**	**3. Was a comprehensive literature search performed?**	**4. Was the status of publication (*i.e.* grey literature) used as an inclusion criterion?**	**5. Was a list of studies (included and excluded) provided?**	**6. Were the characteristics of the included studies provided?**	**7. Was the scientific quality of the included studies assessed and documented?**	**8. Was the scientific quality of the included studies used appropriately in formulating conclusions?**	**9. Were the methods used to combine the findings of studies appropriate?**	**10. Was the likelihood of publication bias assessed?**	**11. Was the conflict of interest stated?**	**AMSTAR**
Motor interventions												
Abdelhaleem	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8
Araújo	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Conner	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	8
De	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	7
De	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8
Klaewkasikum	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8
Liang	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	6
Martins	No	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	6
McLeod	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	6
Merino	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	7
Qian	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	7
Soares	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	No	6
Wang	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	8
Yang	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	7
Zai	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Chen	No	No	No	No	No	Yes	No	Yes	Yes	No	Yes	4
Han	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	8
Hao	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	7

Liu	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	5
Liu	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	7
Arpino	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	4
Stimulation interventions												
Cai	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Chen	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8
Kim	No	Yes	Yes	No	No	No	Yes	Yes	No	No	No	4
Ou	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	6
Saquetto	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	6
Sun	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	7
Zhang	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8
Zhu	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	7
Pulay	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	8
pharmacological interventions												
Albavera	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes	4
Kumar	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	7
Biological interventions												
Eggenberger	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	6
Poh	No	No	Yes	No	No	Yes	No	No	No	No	Yes	3
Qu	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8

Table 3: Grading of Recommendations, Assessment, Development and Evaluation System

Study	Factor	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of the evidence (GRADE)
Motor interventions							
Abdelhaleem	Capacity	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Perceived performance	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Actual performance	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
Araújo	Postural control	Very serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
Conner	6WMT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Gait velocity	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	GMFM-D	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	GMFM-E	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
De	GMFM-all	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM-A	No serious risk of bias	No Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low

	GMFM-B	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM-C	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM-D	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM-E	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
De	FVC	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	FEV1	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	PEF	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	6WMT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	GMF	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Klaewkasikum	Gait improvements: BoNT-A	Very serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Gait improvements: BoNT-A + casting	Very serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Gait improvements: BoNT-A + physiotherapy	Very serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
Liang	GMF	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Medium
	Gait velocity	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Medium
	Muscle strength	Serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Very low
Martins	GMF	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Low
McLeod	GMF	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
Merino	Balance	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Gait velocity	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Spasticity	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	GMF	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Qian	Gait velocity	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Medium
Soares	Aerobic capacity vs Usual care	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Aerobic capacity vs other interventions	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	GMF	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Mobility	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Participation	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low

	Muscle strength	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	ADL	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Wang	GMFM-D	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Medium
	GMFM-E	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Medium
	Balance	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	6MWT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Gait velocity	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Dystonia: MAS	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
Yang	Functional improvement: HABIT-ILE	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Functional improvement: CIMT	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Functional improvement: HABIT	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Functional improvement: M-CIMT	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Functional improvement: AOT	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	Very serious publication bias	Very low
Zai	GMFM-all	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	GMFM-D	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM-E	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
	Balance	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Mobility	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Chen	Arm function	Very serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Serious publication bias	very low
	Postural control	Very serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Serious publication bias	very low
	Ambulation	Very serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	very low
Han	ADL-All	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	High
	ADL: 101-200 min groups	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
	ADL: 201-300 min groups	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
	ADL: 1-100 min groups	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
Hao	Hand function	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low

	GMF	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Grip strength	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Liu	GMF	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
Liu	Balance	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Arpino	GMF	Unclear	No Serious inconsistency	No serious indirectness	No serious imprecision	Unclear	Very low
Stimulation intervention							
Cai	GMFM-D	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
	GMFM-E	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
	TUG	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
	Balance	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
	Ankle-ROM	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low
	6MWT	No serious risk of bias	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	Very low
Chen	Gait velocity	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM D and E	Serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
Kim	Dystonia	Serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	ROM	Serious risk of bias	Very serious inconsistency	No serious indirectness	Serious imprecision	Very serious publication bias	Very low
Ou	Hand function	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Muscle strength	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	Dystonia	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
	Wrist-ROM	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Saquetto	Gait velocity	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	very low
Sun	GMFM-ALL	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM-A	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM-B	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	GMFM-C	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	LOW
	GMFM-D	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low
	FMF	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Serious publication bias	Medium
	MAS	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Very low

	Comprehension	No serious risk of bias	Very serious inconsistency	No serious indirectness	Serious imprecision	Very serious publication bias	Very low
	Language expression	No serious risk of bias	Very serious inconsistency	No serious indirectness	Serious imprecision	Very serious publication bias	Very low
Zhang	GMF	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Serious publication bias	Low
	Developmental quotient	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Serious publication bias	Low
	Comprehension	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Serious publication bias	Low
	Language expression	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Serious publication bias	Low
Zhu	Gait velocity	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
	Step length	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High
Pulay	MAS	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	very low
	Muscle strength	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	very low
Pharmacological intervention							
Albavera	Adverse event: pharyngytis	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Very serious publication bias	very low
	Adverse event: asthma	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Very serious publication bias	very low
	Adverse event: viral upper respiratory tract infection	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Very serious publication bias	very low
	Adverse event: muscle weakness	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Very serious publication bias	very low
	Adverse event: urinary incontinence	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Very serious publication bias	very low
	Adverse event: seizures	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Very serious publication bias	very low
	Adverse event: Fever	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Very serious publication bias	very low
	Adverse event: unspecific pain	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Kumar	Dystonia: MAS	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	Low
Biological intervention							
Eggenberger	GMFM: 6-months	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	very low
	GMFM: 6-12months	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	very low
	GMFM: 12months	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	very low
Qu	GMF	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	very low
	Mental scale	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	very low
	Motor scale	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	very low

	Adverse events	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Very serious publication bias	low

ADL - Activities of daily living, AOT - Action observation training, BoNT-A - botulinum toxin type-A, CIMT - Constraint-induced movement therapy, FEV1 - Forced expiratory volume at 1s, FMF - fine motor function, GMF - gross motor function, HABIT - Hand-arm bimanual intensive training, HABIT-ILE - Hand-arm bimanual intensive training including lower extremity, MAS - Modified Ashworth Scale, M-CIMT - Modified constraint-induced movement therapy, PEF - Peak expiratory flow, ROM - Range of motion, TUG - Timed Up and Go, 6WMT – six-minute walk test.

EFFECTIVENESS OF INTERVENTIONS

Motor Interventions

The results for motor interventions are presented in Tables **4** and **5**. For gross motor function, the total score on the GMFM was reported, along with its five dimensions: A (lying and rolling), B (sitting), C (crawling and kneeling), D (standing), and E (walking, running, and jumping). Task-oriented training exhibited the most substantial effect on the overall GMFM score (SMD = 1.06), followed by aerobic exercise (SMD = 0.70), VR training (SMD = 0.60), and suit therapy (SMD = 0.46). Hippotherapy demonstrated a moderate effect on GMFM-A (SMD = 0.64) and a small effect on GMFM-B (SMD = 0.42). RAGT showed significant effects on both GMFM-D (SMD = 0.84) and GMFM-E (SMD = 0.78), with a smaller effect of hippotherapy noted on GMFM-E (SMD = 0.40). Task-oriented training and VR-therapy were supported by high-quality evidence, while RAGT was backed by a moderate level of evidence. The remaining interventions were supported by low or very low levels of evidence.

VR-training surpassed CT in improving arm function (SMD = 0.86) and hand function (SMD = 0.41), although the overall quality of evidence was low.

Regarding pulmonary function enhancement in CP, only two meta-analyses met the inclusion criteria, focusing on aerobic exercise and respiratory exercises. Aerobic exercise significantly improved aerobic capacity compared to CT but did not show superior efficacy over other interventions specifically targeting aerobic capacity. Respiratory exercises showed improvements in various pulmonary function indicators (small to large effect), but the overall level of evidence was relatively low.

The assessment of movement function in this study encompassed six indicators: postural control, gait velocity, the 6-minute walk test (6WMT), ambulation, mobility, and balance. VR-training demonstrated greater efficacy than CT in improving postural control (SMD = 1.00), ambulation (SMD = 0.76), balance (SMD = 0.47), and 6WMT (SMD = 0.44). Additionally, the combination of RAGT with CT outperformed CT alone in enhancing balance (SMD = 0.91) and 6WMT (SMD = 0.67). Task-oriented training was superior to CT in improving mobility (SMD = 0.68) and balance (SMD = 0.48). Aerobic exercise was found to enhance mobility (SMD = 0.53), while muscle strength training improved balance (SMD = 0.78), with the overall evidence ranging from very low to moderate levels.

In the domain of activity or participation, aerobic exercise was more effective than other interventions in enhancing participation, showing medium effect sizes (SMD = 0.74). Regarding ADL in CP, the impact of VR therapy with varying weekly durations (1-100, 101-200, and 201-300 minutes) was analyzed. Notably, significant improvement in ADL was observed in the group receiving 101-200 minutes of treatment (SMD = 0.44), with this finding supported by a high level of evidence.

In head-to-head comparisons, balance training combined with active intervention significantly outperformed standalone balance training in enhancing posture control (SMD = 1.30). Body-weight supported treadmill training was more effective than other gait-training methods, including treadmill-training (SMD = 0.99), overground gait-training (SMD = 0.42), and RAGT (SMD = 0.41), in improving gait velocity. Additionally, treadmill-training with external cues proved more beneficial than overground gait training (SMD = 0.59), as supported by moderate-level evidence (Table **5**).

Stimulation Interventions

The results for stimulation interventions are detailed in Table **4**. Whole-body vibration training has exhibited a large effect on GMFM-D and E scores (SMD = 1.24), and a medium to large effect on movement function in terms of gait velocity and balance (SMD = 0.71 to 1.37), with this evidence assessed as high in quality.

Functional electrical stimulation has shown significant improvement in step length and gait velocity (SMD = 0.82 to 1.34), with the evidence for these improvements considered to be of high credibility.

Neuromuscular electrical stimulation was found to be more effective than CT or placebo in improving

Table 4: The Effectiveness of Physical, Pharmacological, and Biological Interventions for the Treatment of Cerebral Palsy

Outcomes	Intervention	Controls	Effect metrics	Effect size (95% CI)	Number of RCTs/patients	GRADE
Physical interventions						
Motor intervention						
Body functions and structures						
Gross motor function (mixed-rated)	TOT	CT	SMD	1.06 (0.68 to 1.45)	6/320	Low
	Aerobic exercise	CT	SMD	0.70 (0.21 to 1.19)	6/164	low
	VR	CT	SMD	0.60 (0.34 to 0.87)	7/236	High
	Suit therapy	Not reported	SMD	0.46 (0.10 to 0.82)	4/110	Low
	Exercise intervention	CT	SMD	0.19(-0.22 to 0.59)	27/834	Medium
	Muscle strength training	CT, NT	SMD	0.15 (-0.19 to 0.48)	27/847	Low
	Intensive physiotherapy	Non-intensive physiotherapy	SMD	0.08 (-0.9 to 1.06)	4/226	Very low
	Respiratory exercise + CT	CT	SMD	-0.06 (-1.56 to 1.44)	2/74	Low
Gross motor function: GMFM-A	Hippotherapy	CT, PBO	SMD	0.64 (0.30 to 0.97)	2/146	Low
Gross motor function: GMFM-B	Hippotherapy	CT, PBO	SMD	0.42 (0.09 to 0.75)	2/146	Very low
Gross motor function: GMFM-C	Hippotherapy	CT, PBO	SMD	0.62 (-0.34to 1.59)	2/146	Very low
Gross motor function: GMFM-D	RAGT+CT	CT	SMD	0.84 (0.54 to 1.15)	9/470	Medium
	TOT	CT	SMD	0.54 (0.34 to 0.74)	7/395	Very low
	Hippotherapy	CT, PBO	SMD	0.80 (-0.12 to 1.72)	2/146	Very low
	RAGT	CT	SMD	0.05 (-0.29 to 0.39)	4/135	Low
Gross motor function: GMFM-E	TOT	CT	SMD	1.31 (1.11 to 1.51)	8/440	High
	RAGT+CT	CT	SMD	0.78 (0.43 to 1.14)	9/470	Medium
	Hippotherapy	CT, PBO	SMD	0.40 (0.06 to 0.73)	2/146	Very low
	RAGT	CT	SMD	0.23 (-0.11 to 0.57)	5/135	Low
Upper limb function	HABIT-ILE	PBO	SMD	0.53 (0.09 to 0.96)	22/788	Very low
	CIMT	PBO	SMD	0.44 (0.18 to 0.71)	22/788	Very low
	HABIT	PBO	SMD	0.41 (0.15 to 0.67)	22/788	Very low
	M-CIMT	PBO	SMD	0.39 (0.03 to 0.74)	22/788	Very low
	AOT	PBO	SMD	0.18 (-0.29 to 0.65)	22/788	Very low
Upper limb function: Arm function	VR	CT	SMD	0.86 (0.39 to 1.28)	19/504	Very low
Upper limb function: Hand function	VR	CT	SMD	0.41 (0.14 to 0.68)	4/215	Low
Pulmonary function: aerobic capacity	Aerobic exercise	CT	SMD	0.81 (0.16 to1.47)	4/143	Very low
	Aerobic exercise	Other interventions	SMD	0.05 (-0.09 to 0.70)	2/37	Low
Pulmonary function: FVC	Respiratory exercise + CT	CT	SMD	0.94 (0.90 to 0.97)	3/98	Low
Pulmonary function: FEV1	Respiratory exercise + CT	CT	SMD	0.46 (0.43 to 0.49)	3/98	Low
Pulmonary function: PEF	Respiratory exercise + CT	CT	SMD	0.36 (0.28 to 0.45)	3/98	Low

Movement function: Postural control	VR	CT	SMD	1.00 (0.50 to 1.50)	19/504	very low
Movement function: Gait velocity	RAGT + CT	CT	SMD	0.31 (-0.08 to 0.71)	4/109	Low
	Muscle strength training	CT, NT	SMD	0.13 (-0.62 to 0.32)	27/847	Low
	RAGT	CT	SMD	0.20(-0.18 to 0.57)	5/120	Low
	Exercise intervention	CT	SMD	0.04 (-0.05 to 0.13)	27/834	Medium
Movement function: 6WMT	RAGT + CT	CT	SMD	0.67 (0.18 to 1.15)	3/69	Low
	VR	CT	SMD	0.44 (0.29 to 0.60)	2/137	Low
	Respiratory exercise + CT	CT	SMD	0.29 (-6.30 to 6.87)	3/95	Low
	RAGT	CT	SMD	0.28 (-0.17 to 0.73)	4/77	Low
Movement function: Ambulation	VR	CT	SMD	0.76 (0.35 to 1.16)	19/504	very low
Movement function: Mobility	TOT	CT	SMD	0.68 (0.32 to 1.04)	4/205	Low
	Aerobic exercise	CT	SMD	0.53 (0.05 to 1.05)	4/97	low
Movement function: Balance	RAGT +CT	CT	SMD	0.91 (0.50 to 1.32)	5/379	Very low
	Muscle strength training	CT, NT	SMD	0.78 (0.54 to 1.03)	27/847	Low
	TOT	CT	SMD	0.48 (0.14 to 0.81)	5/381	Very low
	VR	CT	SMD	0.47(0.28 to 0.66)	16/470	Low
Muscle strength	Exercise intervention	CT	SMD	0.45 (0.32 to 0.58)	27/834	Very low
	Aerobic exercise	Other interventions	SMD	0.48 (-0.75 to 1.72)	2/41	Very low
Grip strength	VR	CT	SMD	0.33 (-0.07 to 0.73)	2/99	Low
Dystonia: MAS	RAGT +CT	CT	SMD	-0.67 (0.75 -to 0.41)	5/262	Very low
	Muscle strength training	CT, NT	SMD	0.31 (-0.03 to 0.65)	27/847	Low
Activity or Participation						
Participation	Aerobic exercise	CT	SMD	0.74 (0.10 to 1.39)	2/41	low
Capacity	AOT	PBO, NT	SMD	0.06 (-0.22 to 0.34)	12/257	Very low
Perceived performance	AOT	PBO, NT	SMD	0.30 (–0.28 to 0.89)	2/45	Very low
Actual performance	AOT	PBO, NT	SMD	0.10 (–0.22 to 0.48)	4/108	Very low
ADL-All	VR	Not VR	SMD	0.37 (0.17 to 0.57)	11/442	High
	Aerobic exercise	CT	SMD	0.48 (-0.16 to 0.11)	2/40	low
ADL: 101-200 min groups	VR	Not VR	SMD	0.44 (0.11 to 0.77)	11/442	High
ADL: 201-300 min groups	VR	Not VR	SMD	0.27 (-0.36 to 0.90)	11/442	High
ADL: 1-100 min groups	VR	Not VR	SMD	0.22 (-0.14 to 0.58)	11/442	High
Stimulation interventions						
Body functions and structures						
Gross motor function: GMFM-ALL	rTMS	CT	SMD	1.03 (0.71 to1.35)	11/1653	Very low
	HBOT	CT	SMD	0.29 (0.07 to 0.51)	8/696	Low
Gross motor function: GMFM-A	rTMS	CT	SMD	0.48 (0.40 to 0.55)	6/408	Very low

Gross motor function: GMFM-B	rTMS	CT	SMD	0.48 (0.40 to 0.55)	6/408	Very low
Gross motor function: GMFM-C	rTMS	CT	SMD	0.89 (0.78 to1.01)	6/408	Low
Gross motor function: GMFM-D	rTMS	CT	SMD	1.06 (0.98 to 1.15)	7/448	Very low
	WBV	CT	SMD	0.74 (0.52 to 0.97)	7/202	High
Gross motor function: GMFM-E	rTMS	CT	SMD	1.02 (1.07 to1.33)	7/448	Very low
	WBV	CT	SMD	0.56 (0.15 to 0.98)	7/202	High
Gross motor function: GMFM D and E	NMES	CT, PBO	SMD	1.24 (0.64 to 1.83)	9/302	Very low
Fine motor function: FMFM	rTMS	CT	SMD	0.48 (0.30 to 0.65)	6/532	Medium
Hand function	NMES + CT	CT	SMD	0.80 (0.54 to 1.06)	5/248	Low
Movement function: Step length	FES	CT	SMD	1.34 (1.07 to 1.60)	9/282	High
Movement function: 6WMT	WBV	CT	SMD	0.25 (-14.11 to 14.61)	4/104	Very low
Movement function: Gait velocity	FES	CT	SMD	0.82 (0.57 to 1.07)	9/282	High
	WBV	CT	SMD	0.71 (0.69 to 0.72)	2/46	Very low
	NMES	CT, PBO	SMD	0.29 (0.02 to 0.57)	7/213	Very low
Movement function: Balance	WBV	CT	SMD	1.37 (1.28 to 1.46)	2/130	High
Movement function: TUG	WBV	CT	SMD	-0.68 (-1.08 to 0.27)	4/90	High
Ankle-ROM	WBV	CT	SMD	0.61(-0.77 to 2.00)	2/76	Low
	ESWT	Not ESWT	SMD	0.54 (-1.61 to 2.68)	3/92	Very low
Wrist-ROM	NMES	CT	SMD	0.43 (-0.04 to 0.91)	3/159	Low
Dystonia: MAS	ESWT	Not ESWT	SMD	0.35 (0.22 to 0.47)	5/138	Very low
	rTMS	CT	SMD	0.33 (0.30 to 0.35)	4/483	Very low
	NMES + CT	CT	SMD	0.18 (0.06 to 0.29)	2/75	Low
	WBV + CT	CT	MD	-0.09(-0.33 to 0.15)	3/72	Very low
Muscle strength	NMES + CT	CT	SMD	0.57 (0.25 to 0.88)	3/164	Very low
	WBV + CT	CT	MD	0.52 (-0.20 to 1.25)	3/100	Very low
Developmental quotient	HBOT	CT	SMD	0.95 (0.76 to 1.13)	4/374	Low
Comprehension	HBOT	CT	SMD	0.50 (0.29 to 0.71)	3/270	Low
	rTMS	CT	SMD	0.60(-1.36 to 2.56)	4/288	Very low
Language expression	HBOT	CT	SMD	0.44 (0.22 to 0.65)	3/270	Low
	rTMS	CT	SMD	0.73 (-1.23 to 2.70)	4/288	Very low
Pharmacological interventions						
Body functions and structures						
Gait improvements	BoNT-A	PBO	SMD	1.92 (0.93 to 2.91)	4/175	Very low
Adverse event: pharyngytis	BoNT-A	PBO	RR	7.5 (1.78, 31.61)	20/882	Very low
Adverse event: asthma	BoNT-A	PBO	RR	6.40 (1.20, 34.00)	20/882	Very low
Adverse event: viral upper respiratory tract infection	BoNT-A	PBO	RR	5.91 (1.07, 32.46)	20/882	Very low

Adverse event: muscle weakness	BoNT-A	PBO	RR	5.60 (1.44, 21.84)	20/882	Very low
Adverse event: urinary incontinence	BoNT-A	PBO	RR	5.30 (1.20, 23.52)	20/882	Very low
Adverse event: seizures	BoNT-A	PBO	RR	4.24 (1.85, 9.71)	20/882	Very low
Adverse event: Fever	BoNT-A	PBO	RR	2.77 (1.04, 7.34)	20/882	Very low
Adverse event: unspecific pain	BoNT-A	PBO	RR	2.44 (1.39, 4.27)	20/882	Low
Biological interventions						
Body functions and structures						
Gross motor function (mixed-rated)	SCT	CT, PBO	SMD	0.63 (0.22 to 1.03)	9/646	Very low
Gross motor function: GMFM at 12month	SCT	CT, PBO	SMD	1.33 (0.02 to 2.64)	5/282	Very low
Gross motor function: GMFM at 6month	SCT	CT, PBO	SMD	1.09 (0.22 to 1.96)	5/282	Very low
Gross motor function: GMFM at 6-12 month	SCT	CT, PBO	SMD	0.95 (0.13 to 1.76)	5/282	Very low
Psychological development	SCT	CT, PBO	SMD	0.18 (0.07 to 0.28)	2/96	Very low
Mental development	SCT	CT, PBO	SMD	0.12 (-0.004 to 0.25)	2/96	Very low
Adverse events	SCT	CT, PBO	RR	1.13 (0.90 to 1.42)	20/971	Low

ADL - Activities of daily living, AOT - Action observation training, BoNT-A - Botulinum toxin type A, CIMT - Constraint-induced movement therapy, CI - Confidence interval, CT - conventional treatment, ESWT - Extracorporeal shockwave therapy, FEV1 - Forced expiratory volume at 1s, FES - Functional electrical stimulation, FVC - Forced vital capacity, GMFM - Gross motor function measure, HABIT - Hand-arm bimanual intensive training, HABIT-ILE - Hand-arm bimanual intensive training including lower extremity, HBOT - Hyperbaric oxygen therapy, MAS - Modified Ashworth Scale, M-CIMT - Modified constraint-induced movement therapy, NMES - Neuromuscular electrical stimulation, NT - No treatment, OR - Odds ratio, PEF - Peak expiratory flow, PBO - Placebo, rTMS - Repetitive transcranial magnetic stimulation, RR - Risk ratio, ROM - Range of motion, RAGT - Robot-assisted gait training, SCT - Stem cell therapy, SMD - Standardized mean difference, TOT - Task-oriented training, TUG - Timed Up and Go, VR - Virtual reality, WBV - Whole-body vibration training, 6WMT - Six minute walk test. For effective rate, OR/RR>1 favors the intervention. For adverse event, OR/RR>1 favors the control. SMDs＞0 indicate that intervention is more effective than control.

Table 5: The Effectiveness of Motor and Pharmacological Interventions vs. Active Intervention for the Treatment of Cerebral Palsy

Outcomes	Intervention	Controls	Effect metrics	Effect size (95% CI)	Number of RCTs/patients	GRADE
Motor intervention						
Postural control	BTI+ active intervention	BTI	SMD	1.30 (0.50 to 2.00）	8/194	Very low
Gait velocity	BWSTT	TT	SMD	0.99 (0.98 to 1.10）	15/378	Medium
	BWSTT	CON	SMD	0.77 (0.75 to 0.79）	15/378	Medium
	ECTT	OGT	SMD	0.59 (0.58 to 0.60)	15/378	Medium
	BWSTT	OGT	SMD	0.42 (0.40 to 0.44）	15/378	Medium
	BWSTT	RAGT	SMD	0.41 (0.39 to 0.43）	15/378	Medium
Gross motor function (mixed-rated)	Context-focused therapy	Child-focused therapy	SMD	-0.01 (-0.35 to 0.34)	2/150	Very low
Pharmacological interventions						
Gait improvements	BoNT-A+ Casting	BoNT-A	SMD	0.72 (-0.20 to 1.65)	2/71	Very low

	BoNT-A+ physiotherapy	Physiotherapy	SMD	0.66 (-0.78 to 2.10）	2/75	Very low
	BoNT-A	Casting	SMD	0.16 (-0.48 to 0.80)	2/38	Very low
Dystonia: MAS	BoNT-A	Casting	SMD	0.18 (-0.1 to 0.47)	12/446	Low

BTI - Balance-training interventions, BoNT-A - Botulinum toxin type A, BWSTT - Body weight supported treadmill training, CON - Conventional physical therapy, CT - conventional treatment, ECT - External cues treadmill training, OGT - Over ground gait training, RAGT - Robot-assisted gait training, TT - Treadmill training. SMDs＞0 indicate that intervention is more effective than control.

gross motor function (GMFM-D and E, SMD = 1.24) and gait velocity (SMD = 0.29). When combined with CT, neuromuscular electrical stimulation enhanced hand function (SMD = 0.80) and muscle strength (SMD = 0.57) compared to a control group receiving only CT. However, the overall level of evidence supporting these findings is low or very low.

Hyperbaric oxygen therapy outperformed CT in improving gross motor function (SMD = 0.29), developmental quotient (SMD = 0.95), comprehension (SMD = 0.50), and language expression (SMD = 0.44) in individuals with CP, though the level of evidence for this finding is low.

Compared to CT, rTMS has demonstrated significant improvements on the GMFM total score, including its A, B, C, and D dimensions (small to large effect sizes). Furthermore, rTMS was superior to CT in terms of fine motor function (SMD = 0.48) and dystonia as measured by the MAS (SMD = 0.33), with the overall level of evidence being low or very low.

Pharmacological Interventions

Results for pharmacological interventions are shown in Table **4**. BoNT-A has been found to have a large advantage in improving gait compared to placebo (SMD = 1.92). Overall, the evidence for the effectiveness of pharmacological interventions is quite limited.

Biological Interventions

Results for biological interventions are shown in Table **4**. Studies investigating the effects of stem cell treatment (SCT) showed significant improvements in GMFM scores during the 6-month (SMD = 1.09), 12-month (SMD = 1.33), and 6-12month (SMD = 0.95) follow-up intervals. The level of evidence supporting these conclusions has been evaluated to be very low.

Safety of Interventions

BoNT-A has demonstrated high efficacy in improving gait; however, its use is linked to an increased risk of adverse events [19]. In a study by Qu *et al*.[20], revealing no significant difference in adverse events between the SCT group and the placebo/CT groups, with a relative risk (RR) of 1.13 (0.90 to 1.42). Two additional studie [21, 22] also reported similar results (see Table **4**).

Studies on hyperbaric oxygen therapy [23] indicated that a small number of patients experienced adverse reactions during treatment, with ear pain being the most common side effect. These side effects were mild and resolved after discontinuation of the treatment [24]. RAGT was not associated with significant adverse reactions [25].

DISCUSSION

This umbrella review synthesizes 35 meta-analyses, covering four primary categories of interventions for CP: physical, pharmacological, and biological interventions. It stands as the most comprehensive compilation of existing RCT evidence for CP to date. Furthermore, it integrates efficacy data with safety information, offering evidence-based guidance for clinical decision-making in CP interventions. Figure **1** illustrates the application of the ICF framework in assessing and managing individuals with CP, highlighting its relevance in CP interventions and rehabilitation.

Our findings reveal that assistive devices and technologies like hippotherapy, RAGT, and VR-training are highly effective in improving outcomes such as gross motor function, gait velocity, balance, and dystonia reduction. This review fills the gap in evidence regarding control groups and randomized experiments for RAGT [26], confirming its safety with no significant adverse reactions [25]. Additionally, the review examines the evolving nature of VR training [27] and notes that in CP, the effect sizes for ADLs through VR training vary with weekly intervention duration, following an inverted U-shaped relationship [28], underscoring the importance of adjusting intervention duration in VR-training programs for CP.

This paper highlights the efficacy of "function-based" interventions in motor therapy, which involve targeted exercises to achieve specific goals [29]. For example, task-oriented training is customized to a child's abilities, aiming to improve gross motor function, mobility, and balance [30]. These interventions are underpinned by the principle of neural plasticity, the brain's ability to adapt and reorganize in response to stimulation [31]. Combining enriched environments with specific tasks stimulates non-damaged brain areas, promoting neural pathway formation and reorganization, thus facilitating recovery and functional improvement [32]. Task-oriented training enhances neuroplasticity and motor learning [33], and the use of assistive devices further enriches the rehabilitation environment, increasing patient engagement and motivation [34]. These tools, when combined with tasks, stimulate the neural system and promote functional recovery [35]. However, intervention duration should be carefully managed to provide sufficient stimulation while avoiding fatigue.

For stimulation interventions, hyperbaric oxygen therapy has demonstrated potential in enhancing the developmental quotient, comprehension, and language expression in patients with CP. However, caution is advised when interpreting these findings due to methodological limitations in the study [23]. It's important to note that while minor adverse events such as temporary ear discomfort may occur during intervention, these are generally short-lived and can be managed effectively.

Previous studies have demonstrated that exploiting the nervous system's neuroplasticity significantly enhances motor abilities, as seen in successful upper-limb training programs [26]. However, its application in lower limb training has been less explored. Our research on functional electrical stimulation in lower limb training found notable improvements in stride length and speed [36], indicating its potential in lower limb motor rehabilitation. Similarly, rTMS enhances gross and fine motor functions, likely by modulating motor-related cerebral cortex areas, altering neuronal excitability [37]. Neuromuscular electrical stimulation has also been effective in improving various motor functions and optimizing neuromuscular system performance [38, 39]. These findings suggest the importance of developing tailored devices that effectively stimulate the motor system to match individual capabilities.

For pharmacological interventions, BoNT-A is recognized as the only evidence-based intervention strategy for CP. It is commonly used to manage muscle spasticity and gait disorders and operates by temporarily inhibiting acetylcholine release, thereby reducing spasms and enhancing movement range [40]. While BoNT-A is effective in symptom improvement, it is crucial to consider potential safety concerns, such as pharyngitis, muscle weakness, and seizures [19, 41]. Given these potential adverse events and the lower safety profile of BoNT-A, its application should be undertaken cautiously. However, the overall level of evidence supporting pharmacological interventions for CP is relatively low, attributed to the limited number of studies.

For biological interventions, SCT is emerging as a promising therapy for improving gross motor function and has shown encouraging long-term outcomes [20]. Particularly, the use of umbilical cord blood stem cells is being explored as a potential intervention option for CP, a notion supported by prior research [26]. Furthermore, SCT is generally considered safe. Yet, the development of standardized treatment protocols, including determining the optimal types and dosages of stem cells, requires more extensive and higher-quality RCTs.

Our research found significant differences in the strength of evidence across different intervention categories, with physical interventions (such as RAGT and VR) demonstrating the strongest evidence base. This is primarily attributed to higher research investment (most of the included RCTs involved this field), standardized outcome measures, and a longer research history [14]. Pharmacological interventions (*e.g.*, BoNT-A) exhibit moderate but inconsistent evidence, despite their well-defined biological mechanisms, due to significant industry funding and safety concerns, requiring larger sample sizes [42]. Biological interventions (*e.g.*, SCT) remain in an early stage of development, characterized by heterogeneous research protocols and ethical constraints [43]. These differences reflect variations in research maturity, outcome measurability (motor function is easier to quantify than participation outcomes), commercial viability, and clinical application barriers, highlighting the need for more standardized research protocols and balanced research investment across different intervention types.

Current clinical practice guidelines for CP focus on individualized, multidisciplinary approaches, including physical and pharmacological. Our review corroborates these guidelines, emphasizing the effectiveness of function-based interventions, assistive technologies, and neuroplasticity-exploiting therapies. However, while guidelines support the use of BoNT-A for muscle spasticity, our findings highlight its safety concerns, calling for cautious use and close monitoring. Notably, our review suggests a need for guidelines to further incorporate emerging therapies like stem cell therapy and more personalized rehabilitation programs, considering the social and educational challenges faced by individuals with CP. Additionally, the study underscores the need for further research to establish standardized therapeutic regimens and to rigorously evaluate the long-term safety and efficacy of these interventions. Clinicians can use these findings to inform evidence-based decision-making, tailor treatment plans to individual patient needs, and ultimately improve the quality of life and functional outcomes for individuals with CP. Finally, our analysis provides key insights for multidisciplinary care: Intervention sequences should prioritize low-risk physical therapies and reserve high-risk options (such as BoNT-A) for refractory cases, with a particular focus on participation-oriented outcomes; Team-based implementation must integrate rehabilitation, medical, and psychosocial specialties to cover the full spectrum of the ICF framework; Shared decision-making tools should be incorporated when available, incorporating both motor function data and participation indicators.

This study has several limitations. Firstly, as an umbrella review of published meta-analyses, our analysis inherits the limitations of the constituent studies, including potential publication bias in the original RCTs. While comprehensive search strategies were employed, the exclusion of non-English publications may have introduced language bias, particularly for regionally prevalent interventions. Secondly, the definition of CT varies across studies, typically focusing on improving functionality and utilizing rehabilitation therapies. To address this heterogeneity, although we categorized studies that compare specific active intervention methods separately, enhancing the reliability of intervention comparisons. This challenge was particularly evident in studies from different geographic regions, where most high-income country studies used standardized protocols compared to only a minority of studies from other regions. Thirdly, although CP has diverse clinical presentations [5], most meta-analyses included in this review do not specifically focus on different CP types. However, the majority of the data can still be evaluated within the ICF framework. Fourth, although we included meta-analyses published up to December 2023, some of them may be based on primary RCTs that are now outdated, especially for rapidly evolving interventions like robot-assisted therapy. Finally, while there are no known cures for CP, advancements are being made in preventing and ameliorating physical impairments. Yet, there is a notable lack of research on the activities and participation of individuals with CP. This gap may be attributed to the difficulties in assessing and evaluating these aspects, along with an incomplete exploration of intervention effects across different behavioral domains. Further attention and research are needed in this area.

CONCLUSION

Our findings demonstrate that while assistive technologies (*e.g.*, RAGT), biological interventions (*e.g.*, SCT), and pharmacological interventions (*e.g.*, BoNT-A) show promise in CP management, their clinical implementation remains hampered by inconsistent protocols and heterogeneous outcome measures. To address these challenges and translate evidence into practice, we call for (1) standardized reporting through international consensus to unify outcome measures (*e.g.*, adopting Core Outcome Sets for CP trials) and intervention dosages; (2) development of risk-stratified clinical pathways that balance efficacy with safety profiles, reserving higher-risk interventions (*e.g.*, BoNT-A) for cases unresponsive to conservative therapies; and (3) prioritization of research on understudied domains (*e.g.*, participation outcomes) and emerging combination therapies (*e.g.*, VR-pharmacological approaches) [44, 45]. This demands a paradigm shift from isolated interventions to integrated, patient-centered models that equally prioritize clinical utility, safety monitoring, and social participation - achievable only through collaborative efforts where researchers standardize evidence generation, clinicians adopt stratified approaches, and policymakers fund implementation studies to optimize lifelong outcomes for individuals with CP.

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