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SYSTEMATIC REVIEW

Overview of Cochrane systematic reviews for rehabilitation interventions in individuals with cerebral palsy: A mapping synthesis

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Abstract

Aim: This overview of Cochrane systematic reviews (CSRs) reports on current evidence on the effectiveness of rehabilitation interventions for individuals with cerebral palsy (CP) and the quality of the evidence.

Method: Following the inclusion criteria defined by the World Health Organization, all CSRs tagged in the Cochrane Rehabilitation database that were relevant for individuals with CP were included. A mapping synthesis was used to group outcomes and comparisons of included CSRs indicating the effect of rehabilitation interventions and the certainty of evidence.

Results: A total of eight CSRs were included in the evidence map. The effect of interventions varied across comparisons and the certainty of evidence was inconsistent, ranging from high to very low. The best evidence was found for botulinum neurotoxin A (BoNT-A) combined with occupational therapy in the management of spasticity. However, the effect of BoNT-A on drooling and salivation remains unclear. A paucity of randomized controlled trials studying treatments for both dystonia and postural deformities was noted.

Interpretation: This review emphasizes the need to further investigate the effectiveness and cost–benefit of rehabilitation interventions for individuals with CP.

Abbreviations: CIMT, constraint-induced movement therapy; CSR, Cochrane systematic review; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LMIC, low- and middle-income country; WHO, World Health Organization.

[Correction added on 5 April 2023, after first online publication: The affiliation for Carlotte Kiekens has been updated.]

Access to rehabilitation is a critical component for achieving universal health care. However, lack of access to facilities offering rehabilitation services remains a critical issue, in particular in low- and middle-income countries (LMICs).[1] To date, one in three people lives with a condition that may benefit from rehabilitation, while rehabilitation is often viewed as an optional treatment and only a small portion of these patients access rehabilitation services.[1] In 2017, the World Health Organization (WHO) launched 'Rehabilitation 2030: a Call for Action', which aimed to scale up rehabilitation worldwide and integrate rehabilitation services into health systems.[2] As part of this initiative, the WHO Rehabilitation Programme is developing a prioritized set of evidence-based interventions, called the Package of Interventions for Rehabilitation, for 20 health-relevant conditions.[3,4] The Package of Interventions for Rehabilitation development consists of six phases organized in a stepwise manner, including a 'Best Evidence for Rehabilitation' (be4rehab) phase, to identify best-quality evidence on the effectiveness of rehabilitation interventions for different health conditions, including cerebral palsy (CP).

CP refers to a group of permanent disorders associated with non-progressive brain injury or abnormalities of brain areas involved in motor function and posture, acquired during the antenatal, perinatal, or early postnatal period.[5–7] With an incidence of 1.5 to 3.0 per 1000 live births, CP is the most common physical disability among children.[8] In Europe, a multi-site population-based study recorded a decline in the incidence of CP from 1.90 per 1000 live births in 1980 to 1.77 per 1000 live births in 2003.[9] A similar decrease in the incidence rate has been recorded in Australia.[10] However, studies in LMICs have published higher prevalence rates of CP, with an overall birth prevalence of 3.4 per 1000 births, in particular 2.9 per 1000 births and 3.6 per 1000 births reported in Uganda and Egypt respectively, compared with 1.8 to 2.3 per 1000 births observed in Europe, Australia, and the USA.[11,12] This view is probably limited because data from LMICs may originate from few studies representing only a handful of countries[13] and the incidence of CP in LMICs is probably underestimated.[14] Moreover, recent incidence rates in several high-income countries have not yet been published and the USA does not have a centralized system for tracking the incidence of CP.

The core manifestations of CP are motor disorders. According to the Surveillance of Cerebral Palsy in Europe, CP is classified based on the patient's predominant motor symptoms as spastic (unilateral or bilateral), dyskinetic (dystonic or choreoathetosis), and ataxic.[6] Additional conditions associated with CP include but are not limited to intellectual disability, epilepsy, musculoskeletal disorders, and speech and swallowing impairments.[7] An early diagnosis of CP is strongly encouraged, particularly in infants born preterm, or in patients with low birthweight, to promote timely medical and rehabilitative interventions aiming to improve as many motor and cognitive functions as possible through brain plasticity.[5]

However, a multicentre study analysing epidemiology and access to rehabilitation services for individuals with CP determined that the median age of diagnosis is 3 years in LMICs, where only 53% of children with CP receive proper rehabilitation management.[15] Delay in diagnosis and access to rehabilitation induce a cascade effect leading to a worsening of motor function and the development of secondary complications, including joint and bone deformities, malnutrition, higher premature mortality, and an overall reduced life expectancy.[11,16]

Considering that Cochrane systematic reviews (CSRs) are the criterion standard among systematic reviews due to their high-quality methodology,[17] the aim of this overview was to synthesize evidence from CSRs using an evidence map, to collect the most reliable evidence for rehabilitation interventions in individuals with CP.

What this paper adds

- The quality and quantity of evidence on rehabilitation interventions for cerebral palsy is limited worldwide.
- Botulinum neurotoxin A plus occupational therapy showed robust efficacy for the management of upper-limb spasticity.
- Evidence on sleep-positioning systems for hip migration and trihexyphenidyl for dystonia is scarce.

METHOD

We performed an overview of CSRs that addressed the effectiveness of rehabilitation interventions for individuals with CP and we synthesized the findings using a mapping synthesis methodology. The overview was conducted according to the methods framed by the WHO Rehabilitation Programme and Cochrane Rehabilitation and was approved by the WHO Guidelines Review Committee.[4] The authors used an evidence map to compile the characteristics of each review, including a ranking of certainty of evidence. The overview adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18] and was registered.

Search strategy

The search strategy was based on the methodology developed by the WHO and Cochrane Rehabilitation for the WHO Package of Interventions for Rehabilitation.[19,20] The WHO Rehabilitation Programme Advisory Board selected the health conditions in the summer of 2018, based on the disability statistics of the Global Burden of Disease Study[21] and expert opinion. It was performed according to the two following criteria: (1) to be amenable to rehabilitation and (2) to cover different disease areas (e.g. musculoskeletal, cardiovascular,

TABLE 1 AMSTAR 2 quality assessment of Cochrane systematic reviews.

	Hoare et al.[32]	Harvey et al.[31]	Ryan et al.[30]	Blake et al.[29]	Walshe et al.[28]	Hoare et al.[27]	Blumetti et al.[33]	Chiu et al.[34]
(1) Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(2) Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(3) Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(4) Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(5) Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(6) Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(7) Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(8) Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(9) Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(10) Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No	No	No	No
(11) If a meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(12) If a meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(13) Did the review authors account for risk of bias in individual studies when interpreting or discussing the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(14) Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(15) If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(16) Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviation: AMSTAR 2, A MeaSurement Tool to Assess systematic Reviews; PICO, patient/population, intervention, comparison, and outcomes.

nervous system). In addition, the level of disability associated with these health conditions, and prevalence estimates, were also considered.[20] The CSR search was led by the Cochrane Rehabilitation team using the tagging process.[22] The search strings consisted of terms defining the 'health condition', in this case 'cerebral palsy' and 'rehabilitation', and run in the Cochrane Library. A Cochrane Rehabilitation team extracted the full citations, including abstracts, of all CSRs and protocols published from the inception of the Cochrane Library (1996) to 31st August 2019, importing these into a Knack database

(https://www.knack.com) to be tagged by 'tagging reviewers'.[22] They selected the CSRs relevant to rehabilitation using the following criterion: all reviews on interventions provided or prescribed by rehabilitation professionals.[22] The CSRs relevant to rehabilitation are constantly updated in an online database (https://rehabilitation.cochrane.org/evidence). The search for the WHO was run in August 2019, with an updated search through the Cochrane Library in June 2022.

Assessment of methodological quality of included reviews

We used the 16-item A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) to assess the methodological quality of the included CSRs. AMSTAR 2 is a binary (yes or no) instrument containing 16 items that does not generate an overall score. The overall rating is based on weaknesses in seven critical domains.[23] We adopted the process of considered judgement to (1) interpret weaknesses detected by these critical items and (2) reach a consensus on the methodological quality of the included reviews. Two independent assessors (MP, EP) critically appraised the included CSRs to interpret weaknesses detected by these critical items and to reach a consensus on the methodological quality. Any disagreement was solved through discussion with a third assessor (SL).

Data extraction and certainty of evidence appraisal

The authors identified and extracted data from the table of findings published in each CSR. For all rehabilitation-relevant interventions, the following data were collected and entered into an Excel spreadsheet: type of outcome; outcome measure(s); number of primary studies included; sample size; population; intervention; comparators; effect (i.e. in favour of intervention, in favour of control, no effect); and the certainty of evidence judgement for each comparison and outcome.

Furthermore, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) judgement reported in each CSR was extracted. When this judgement was missing in a CSR, two authors (MP, EP) independently appraised the certainty of evidence for the primary outcomes using the standard GRADE approach.[24,25] In the event of disagreement between two authors, a consensus was achieved through discussion with a third author (SL). This post hoc GRADE process consisted of two steps: (1) retrieval of the original primary studies included in each CSR and (2) tabulation of the judgements in Summary of Findings tables using the GRADEPro software (GRADEproGDT, Evidence Prime, European Union).

Summarizing evidence within a map

We summarized the results using tabular features identified as 'mapping synthesis', a methodology commonly used to provide a comprehensive and user-friendly interface of current knowledge and gaps.[26] An Excel spreadsheet was used to map the evidence, grouping outcomes and comparisons of the included CSRs indicating the effect (no effect, in favour of intervention, in favour of control) and the quality of evidence (very low, low, moderate, and high) to facilitate the understanding of the clinical effect of the rehabilitation intervention. We did not use this evidence mapping to identify evidence gaps, nor did we examine other outcomes and interventions in addition to those already studied in the included CSRs.

RESULTS

Two hundred and forty-eight CSRs published between August 2009 and August 2019 have been tagged in the Cochrane Rehabilitation database. Of these, six met the inclusion criteria set by the WHO. The new search performed in the Cochrane Library in June 2022 identified two additional reviews leading to a total of eight CSRs related to CP included in this overview.[27–34] Table S1 shows the main characteristics of the CSRs included in this review.

The results of the AMSTAR 2 assessment indicated a high methodological quality of all eight CSRs, even in cases where information about funding sources was not disclosed (Table 1).

All the reviews were evaluated for certainty of evidence using the GRADE approach.[27–34] The included CSRs reviewed interventions to treat the following rehabilitative needs in patients with CP: upper- and lower-limb spasticity with botulinum neurotoxin A (BoNT-A); different types of exercise for gross motor function; constraint-induced movement therapy (CIMT) for bimanual performance; mechanically assisted walking training to improve walking; participation and quality of life; pharmacological interventions for drooling and dystonia; and a sleep-positioning system to reduce or prevent hip migration in this population. Studies examining children and adolescents (from birth to 19 years old) of both sexes were included in six CSRs; two CSRs[30,31] included trials examining children, adolescents, and adults diagnosed with CP. Results were grouped by outcomes and reported below according to the main domains of the Comprehensive Core Sets of the International Classification of Functioning, Disability and Health (ICF) for CP: 'body functions and structures' and 'activity and participation'.[35] We arbitrarily reported the most appropriate ICF categories, taking into account that the outcome measures used in the CSRs analysed may cover multiple ICF categories. Considering the number of comparisons, the findings were collated into two evidence maps to increase readability, dividing the interventions into pharmacological (Figure 1) and non-pharmacological (Figure 2).

High- and moderate-certainty evidence

The highest certainty of evidence was found in three CSRs: two CSRs examined the effectiveness of intramuscular

Comparison	Placebo/sham/usual care/nothing										Other treatments								
Treatment	Trihexyphenidy	Benzotropine	Glycopyrolate	BoNT-A					BoNT-A/occupational therapy		BoNT-A				BoNT-A/occupational therapy			High-dose BoNT-A	
Drooling		LOW (6)	LOW (9)	LOW (12–14)		LOW (15)	LOW (17)				LOW (47)	LOW (48)		LOW (49)					
Spasticity				VERY LOW (18)	MODERATE (19)	VERY LOW (20)	MODERATE (21)	MODERATE (22)	HIGH (40)	MODERATE (41)	VERY LOW (50)	HIGH (51)	LOW (52)	MODERATE (53)	HIGH (65, 66)	MODERATE (67)		NA (78)	NA (79)
Dystonia	VERY LOW (1)																		
Range of motion				VERY LOW (23)		MODERATE (24)	VERY LOW (25)				VERY LOW (54)		LOW (55)						
Quality of movement				MODERATE (26)					MODERATE (42)	MODERATE (43)	MODERATE (56)				HIGH (68,69)	MODERATE (70)	HIGH (71)	NA (80)	MODERATE (81)
Gait				VERY LOW (27)			MODERATE (28, 29)				LOW (57)		MODERATE (58)						
Function				VERY LOW (30)		MODERATE (31)	MODERATE (32)				VERY LOW (59)		MODERATE (60)						
Performance	LOW (2)			HIGH (33)					HIGH (44)		MODERATE (61)				HIGH (72)		MODERATE (73)	NA (82)	
Goal attainment				MODERATE (34)					HIGH (45)		MODERATE (62)				HIGH (74, 75)			NA (83)	
Satisfaction				MODERATE (35)			MODERATE (36)												
Occupational satisfaction				HIGH (37)					HIGH (46)		MODERATE (63)				HIGH (76)		MODERATE (77)	NA (84)	
Participation	LOW (3)																		
Non-compliance	low (4)	low (7)	low (10)	low (38)							low (64)								
Adverse effects	LOW (5)	low (8)	low (11)	low (39)															

BoNT-A injections into upper- and lower-limb muscles respectively,[27,33] while a third CSR synthesized the effects of mechanically assisted walking training with and without body weight support.[34]

Body function and structure

Spasticity

Spasticity includes muscle tone functions (b735) and range of motion (mobility of joint functions, [b710]).

Compared to placebo or no treatment, BoNT-A alone probably has no effect on elbow and wrist flexor spasticity (moderate certainty evidence) that can be estimated[29] and probably improves ankle plantar flexor spasticity and passive ankle range of motion at the short-term follow-up (moderate certainty evidence);[33] BoNT-A in association with occupational therapy interventions (e.g. principles of motor skills learning, occupational performance and goal attainment, activities for upper-extremity strengthening and development of skills for daily living) improves wrist flexor spasticity (high certainty evidence) but it probably has no effect on elbow flexor spasticity (moderate certainty evidence).[29]

Compared with occupational therapy, BoNT-A alone improves elbow flexor spasticity and probably has no effect on wrist flexor spasticity (high-to-moderate-certainty evidence), while BoNT-A combined with occupational therapy improves elbow and wrist flexor spasticity (high certainty evidence).[27]

When compared to BoNT-A alone, BoNT-A in association with occupational therapy improves wrist flexor spasticity; however, it probably has no effect on elbow flexor spasticity (high- to moderate-certainty evidence).[27]

Activity and participation

Occupational performance

Occupational performance includes satisfaction, activity-level goal attainment, participation (i.e. carrying out daily routine [d230], hand and arm use [d445], caring for body parts [d520], basic interpersonal interactions [d710], school education [d820], community life [d910], recreation and leisure [d920]).

Compared with placebo or no treatment, BoNT-A alone increases goal attainment (moderate certainty of evidence) and satisfaction (high certainty of evidence) in occupational performance; BoNT-A combined with occupational therapy improves performance (high certainty evidence).[27]

Compared to occupational therapy alone, BoNT-A probably has no effect on performance, activity-level goal attainment, or satisfaction in occupational performance (moderate certainty evidence); however, BoNT-A in conjunction with occupational therapy improves activity-level goal attainment and satisfaction in occupational performance (high certainty evidence).[27]

Finally, when compared to BoNT-A alone, BoNT-A combined with occupational therapy probably has no

FIGURE 1 Evidence map for pharmacological interventions in individuals with cerebral palsy. Map colors: white: favour intervention; black: favour comparison; light grey UPPERCASE: no effect; dark grey lowercase: could not be estimated. Outcomes legend: (1) outcome: BADS; comparison: placebo; (2) outcome: performance; comparison placebo; (3) outcomes: GAS, COPM-satisfaction, and COPM-performance; comparison placebo; (4) outcome: non-compliance with intervention; comparison placebo; (5) outcome: adverse effects; comparison placebo; (6) outcomes: reduction in salivary flow and reduction in frequency and severity of drooling (Teacher's Drool Scale); comparison placebo; (7) outcome: non-compliance with intervention; comparison placebo; (8) outcome: adverse effects; comparison placebo; (9) outcome: adaptation of Thomas's reduction in frequency and severity of drooling (Thomas–Stonell and Greenberg Scale); comparison placebo; (10) outcome: non-compliance with intervention; comparison placebo; (11) outcome: adverse effects; comparison placebo; (12) outcomes: reduction in salivary flow (aa), reduction in frequency and severity of drooling (Drooling Quotient-b and Thomas–Stonell and Greenberg Scale); comparison placebo; (13) outcome: reduction in frequency and severity of drooling (Drooling Impact Scale-4 weeks); comparison no intervention; (14) outcomes: reduction in frequency and severity of drooling (Drooling Quotient-b and bb; Drooling Quotient**); comparison usual care; (15) outcome: reduction in salivary flow (a), reduction in frequency and severity of drooling (Drooling Quotient-bb); comparison placebo; (16) outcome: reduction in frequency and severity of drooling (Drooling Quotient-baseline); comparison placebo; (17) outcome: reduction in frequency and severity of drooling (Drooling Quotient-baseline); comparison placebo; (18) outcomes: spasticity-ankle plantar flexors (mt and lt); comparison usual care/physiotherapy; (19) outcomes: spasticity-ankle plantar flexors (st and mt); comparison placebo/sham; (20) outcome: spasticity-ankle plantar flexors (ST); comparison usual care/physiotherapy; (21) outcome: spasticity-ankle plantar flexors (lt); comparison placebo/sham; (22) outcomes: elbow flexor and wrist flexor spasticity; comparison placebo/no treatment; (23) outcomes: passive ankle range of motion (st and lt); comparison usual care/physiotherapy; (24) outcomes: passive ankle range of motion (st, mt, and lt); comparison placebo/sham; (25) outcome: passive ankle range of motion (mt); comparison usual care/physiotherapy; (26) outcomes: quality of movement (18 months–8 years) and (5–15 years); comparison placebo/no treatment; (27) outcome: observational gait analysis (mt); comparison usual care/physiotherapy; (28) outcomes: instrumented gait analysis (st) and observational gait analysis (st); comparison placebo or sham; (29) outcome: observational gait analysis (mt); comparison no intervention; (30) outcomes: function (st, mt, and lt); comparison usual care or physiotherapy; (31) outcomes: function (mt and lt); comparison placebo or sham; (32) outcome: function (st); comparison placebo/sham; (33) outcome: performance; comparison placebo/no treatment; (34) outcome: goal attainment; comparison placebo/no treatment; (35) outcomes: satisfaction (st and mt); comparison placebo/sham; (36) outcome: satisfaction (lt); comparison placebo or sham; (37) outcome: occupational performance-satisfaction; comparison placebo/no treatment; (38) outcome: non-compliance with intervention; comparison placebo; (39) outcome: adverse effects to BoNT-A; comparison placebo; (40) outcome: wrist flexor spasticity; comparison placebo or no treatment; (41) outcome: elbow flexor spasticity; comparison placebo/no treatment; (42) outcome: quality of movement (18 months–8 years); comparison placebo or no treatment; (43) outcome: quality of movement (5–15 years); comparison placebo/no treatment; (44) outcome: performance; comparison placebo or no treatment; (45) outcome: goal attainment; comparison placebo or no treatment; (46) outcome: occupational performance-satisfaction; comparison placebo or no treatment; (47) outcomes: reduction in salivary flow (swab method-c) and reduction in frequency and severity of drooling (Drooling Quotient-dd); comparison scopolamine; (48) outcomes: reduction in salivary flow (swab methods-cc) and reduction in frequency and severity of drooling (Drooling Quotient-24 weeks); comparison scopolamine; (49) outcome: reduction in frequency and severity of drooling (Drooling Quotient-d); comparison scopolamine; (50) outcome: spasticity (hip adductors-mt); comparison orthoses; (51) outcome: elbow flexor spasticity; comparison occupational therapy; (52) outcome: spasticity-ankle plantar flexors (st, mt, and lt); comparison serial casting; (53) outcome: wrist flexor spasticity; comparison occupational therapy; (54) outcome: passive hip adduction range of motion (mt); comparison orthoses; (55) outcome: passive ankle range of motion (st, mt, and lt); comparison serial casting; (56) outcome: quality of movement (18 months–8 years) and (5–15 years); comparison occupational therapy; (57) outcome: instrumented gait analysis (st and mt); comparison serial casting; (58) outcomes: instrumented gait analysis (lt) and observational gait analysis (st, mt, and lt); comparison serial casting; (59) outcome: function (mt); comparison orthoses; (60) outcome: function (st, mt, and lt); comparison serial casting; (61) outcome: performance; comparison occupational therapy; (62) outcome: goal attainment; comparison occupational therapy; (63) outcome: occupational performance-satisfaction; comparison occupational therapy; (64) outcome: non-compliance with intervention; comparison scopolamine; (65) outcomes: elbow flexor spasticity and wrist flexor spasticity; comparison occupational therapy; (66) outcome: wrist flexor spasticity; comparison BoNT-A; (67) outcome: elbow flexor spasticity; comparison BoNT-A; (68) outcome: quality of movement (5–15 years); comparison BoNT-A; (69) outcome: quality of movement (18 months–8 years); comparison occupational therapy; (70) outcome: quality of movement (18 months–8 years); comparison BoNT-A; (71) outcome: quality of movement (5–15 years); comparison occupational therapy; (72) outcome: performance; comparison occupational therapy; (73) outcome: performance; comparison BoNT-A; (74) outcome: goal attainment; comparison occupational therapy; (75) outcome: goal attainment; comparison BoNT-A; (76) outcome: occupational performance-satisfaction; comparison occupational therapy; (77) outcome: occupational performance-satisfaction; comparison BoNT-A; (78) outcome: elbow flexor spasticity; comparison low-dose BoNT-A; (79) outcome: wrist flexor spasticity; comparison low-dose BoNT-A; (80) outcome: quality of movement (5–15 years); comparison low-dose BoNT-A; (81) outcome: quality of movement (18 months–8 years); comparison low-dose BoNT-A; (82) outcome: performance; comparison low-dose BoNT-A; (83) outcome: goal attainment, comparison low-dose BoNT-A; (84) outcome: occupational performance-satisfaction; comparison low-dose BoNT-A. a: (baseline) 0–2, 4, 8, 10, 14, 18, 22 weeks; aa: 6, 12 weeks; b: 0–2, 4, 6, 8, 12 weeks; bb: 10, 14, 18, 22 weeks; c: 0–2, 4, 8, weeks; cc: 16, 24 weeks; d: 2, 8 weeks; dd: 4, 16 weeks. *: 0–2 weeks scopolamine versus baseline, **: 2, 4, 8, 16, 24 weeks BoNT-A versus baseline. Abbreviations: BADS, Barry–Albright Dystonia Scale; BoNT-A, botulinum neurotoxin A; COPM, Canadian Occupational Performance Measure; CP, cerebral palsy; GAS, goal attainment scale; NA, not applicable. st: short-term follow-up; mt: medium-term follow-up; lt: long-term follow-up.

effect on performance and satisfaction (moderate certainty evidence); however, the combined interventions improve activity-level goal attainment (high certainty evidence).[27]

Compared to the same dose of overground walking training, mechanically assisted walking training without body weight support probably improves participation while no difference was found for the same outcome with mechanically assisted walking training with body weight support (moderate certainty evidence).[33]

Gross motor function

Gross motor function includes walking (d450) and moving around (d455). Compared with placebo or sham therapy, BoNT-A improved satisfaction and had a small positive effect on functional mobility at the medium-term follow-up. BoNT-A is not more effective than placebo, sham, or serial casting in improving functional mobility at the short-term or long-term follow-up (moderate certainty evidence).[33] BoNT-A is not more effective than serial casting in improving

Comparison	Usual care, placebo, sham, no treatment				Other treatments									
Treatment	Physical exercise		Mechanically assisted walking training		CIMT					Resistance training	Sleeping in sleep-positioning system	Mechanically assisted walking training		
Pain											very low (42)			
Sleep											very low (43)			
Hip problems											NA (44)			
Motor function	LOW (1)	LOW (2, 3)	LOW (7)	LOW (8)						LOW (41)		MODERATE (48)	LOW (49)	
Gait	VERY LOW (4)	LOW (5)	MODERATE (9, 10)									MODERATE (50)	LOW (51)	
Physical functioning											NA (45)			
Manual ability					VERY LOW (17)	LOW (18)	VERY LOW (19–22)	LOW (23, 24)	NA (25–28)					
Self-care					NA (29,30)			VERY LOW (31)	LOW (32)					
Performance					NA (33,34)			LOW (35)	VERY LOW (36)					
Participation	LOW (6)		NA (11)	LOW (12)								MODERATE (52)	MODERATE (53)	
Quality of life			NA (13)	LOW (14)							NA (46)	NA (54, 55)		
Adverse effects			LOW (15, 16)		NA (37–40)						NA (47)	NA (56, 57)		

gross motor function at any follow-up (moderate certainty evidence).[33]

Compared with the same dose of overground walking training, mechanically assisted walking training without body weight support probably improves gross motor function (moderate certainty evidence).[34]

Upper-limb quality of movement

Upper-limb quality of movement includes hand and arm use (d445). Compared with occupational therapy alone, BoNT-A probably has no effect on upper-limb quality of movement. When BoNT-A is associated with occupational therapy, compared to placebo or no treatment, it probably improves the quality of movement measured with the Quality of Upper Extremity Skills Test, although it has no effect on the quality of movement measured via the Melbourne Assessment scale (all moderate-certainty evidence). Compared to occupational therapy alone, BoNT-A in conjunction with occupational therapy improves quality of movement when assessed with the Quality of Upper Extremity Skills Test (high certainty evidence).[27] The combined interventions, when compared to BoNT-A alone, improve quality of movement when assessed with the Melbourne Assessment scale (high certainty evidence).[27]

Gait scores and walking speed

Gait scores and walking speed includes walking (d450). Compared with placebo or sham treatment, BoNT-A probably improves overall gait scores at the short- and medium-term follow-ups (moderate certainty evidence). However, no differences in gait scores were observed at all follow-up intervals when BoNT-A was compared to serial casting (observational gait analysis) (moderate certainty evidence).[33]

Compared with no walking training or the same dose of overground walking training, mechanically assisted walking training without body weight support probably increases walking speed (moderate certainty evidence).[34] Similarly, mechanically assisted walking training with body weight support increases walking speed compared with no walking training (moderate certainty evidence).[34]

Low and very low certainty evidence

The remaining pharmacological and non-pharmacological interventions for CP provided low to very low certainty evidence in several comparisons.[28–32]

Body function and structure

Sleep patterns include sleep functions (b134) and pain (sensation of pain, b280). It is uncertain whether sleeping in a sleep-positioning system has an effect on sleep patterns and pain compared to not sleeping in a sleep-positioning system (not estimable, very low certainty evidence).[29] None of the randomized control trials included in the CSRs investigated the effect of sleeping in a sleep-positioning system on hip migration reduction.[29]

FIGURE 2 Evidence map for non-pharmacological interventions in persons with cerebral palsy. Map colours: white: favour intervention; black: favour comparison; light grey UPPERCASE: no effect; dark grey lowercase: could not be estimated. Outcomes legend: (1) outcome: GMFM; treatment aerobic exercise, comparison usual care; (2) outcome: GMFM; treatment mixed training, comparison usual care; (3) outcome: GMFM (short- and intermediate-term); treatment resistance training, comparison usual care; (4) outcome: gait speed; treatment aerobic exercise, comparison usual care; (5) outcome: gait speed (short- and intermediate-term); treatment resistance training, comparison usual care; (6) outcome: participation; treatment resistance training, comparison usual care; (7) outcome: GMFM; treatment mechanically assisted walking training without body weight support, comparison no walking training; (8) outcome: GMFM; treatment mechanically assisted walking training with body weight support, comparison no walking training; (9) outcome: mobility (gait analysis); treatment mechanically assisted walking training without body weight support, comparison no walking training; (10) outcome: mobility (10 Meter Walk Test); treatment mechanically assisted walking training with body weight support, comparison no walking training; (11) outcome: participation; treatment mechanically assisted walking training without body weight support, comparison no walking training; (12) outcome: participation; treatment mechanically assisted walking training with body weight support, comparison no walking training; (13) outcome: quality of life; treatment mechanically assisted walking training without body weight support, comparison no walking training; (14) outcome: quality of life (PedsQL-CP score); treatment mechanically assisted walking training with body weight support, comparison no walking training; (15) outcome: adverse effects; treatment mechanically assisted walking training without body weight support, comparison no walking training; (16) outcome: adverse effects; treatment mechanically assisted walking training with body weight support, comparison no walking training; (17) outcome: unimanual capacity (QUEST); low-dose comparison; (18) outcome: bimanual performance; low-dose comparison; (19) outcome: unimanual capacity (QUEST); low-dose comparison; (20) outcomes: unimanual capacity (Melbourne Assessment) and unimanual capacity (QUEST); high-dose comparison; (21) outcome: unimanual capacity (QUEST) and manual ability; dose-matched comparison; (22) outcomes: bimanual performance (Kids-Assisting Hand Assessment from −10.26 to 8.73), bimanual performance, unimanual capacity (QUEST); comparison different forms CIMT; (23) outcome: bimanual performance; high-dose comparison; (24) outcome: bimanual performance and unimanual capacity (Melbourne Assessment); dose-matched comparison; (25) outcome: manual ability; low-dose comparison; (26) outcome: manual ability; high-dose comparison; (27) outcome: manual ability; dose-matched comparison; (28) outcomes: unimanual capacity (Melbourne Assessment) and manual ability; comparison different form CIMT; (29) outcome: self-care; low-dose comparison; (30) outcome: self-care; comparison different forms CIMT; (31) outcome: self-care; high-dose comparison; (32) outcome: self-care; dose-matched comparison; (33) outcome: performance; low-dose comparison; (34) outcome: performance; comparison different forms CIMT; (35) outcome: performance; high-dose comparison; (36) outcome: performance; dose-matched comparison; (37) outcome: adverse effects; low-dose comparison; (38) outcome: adverse effects; comparison different forms CIMT; (39) outcome: adverse effects; high-dose comparison; (40) outcome: adverse effects; dose-matched comparison; (41) outcome: GMFM; comparison aerobic exercise; (42) outcome: effect on pain; comparison not sleeping in sleep positioning system; (43) outcome: effect on sleep pattern and quality; comparison not sleeping in sleep-positioning system; (44) outcome: reduce hip migration and hip problems; comparison not sleeping in sleep-positioning system; (45) outcome: effect on physical functioning; comparison not sleeping in sleep-positioning system; (46) outcome: effect on quality of life of child and family; comparison not sleeping in sleep-positioning system; (47) outcome: adverse effects; comparison not sleeping in sleep-positioning system; (48) outcome: GMFM; treatment mechanically assisted walking training without body weight support, comparison same dose of overground walking training; (49) outcome: GMFM; treatment mechanically assisted walking training with body weight support, comparison same dose of overground walking training; (50) outcome: mobility (6 Minute Walk Test or gait analysis); treatment mechanically assisted walking training without body weight support, comparison same dose of overground walking training; (51) outcome: mobility (10 Meter Walk Test); treatment mechanically assisted walking training with body weight support, comparison same dose of overground walking training; (52) outcome: participation (PEDI); treatment mechanically assisted walking training without body weight support, comparison same dose of overground walking training; (53) outcome: participation (SFA score); treatment mechanically assisted walking training with body weight support, comparison same dose of overground walking training; (54) outcome: quality of life; treatment mechanically assisted walking training without body weight support, comparison same dose of overground walking training; (55) outcome: quality of life; treatment mechanically assisted walking training with body weight support, comparison same dose of overground walking training; (56) outcome: adverse effects; treatment mechanically assisted walking training without body weight support, comparison same dose of overground walking training; (57) outcome: adverse effects; treatment mechanically assisted walking training with body weight support, comparison same dose of overground walking training. Abbreviations: CIMT, constraint-induced movement therapy; CP, cerebral palsy; GMFM, gross motor function measure; NA, not applicable; PEDI, Pediatric Evaluation of Disability Inventory; PedsQL-CP, Pediatric Quality of Life Inventory-CP module; SFA, School Function Assessment. st, short-term follow-up; mt, medium-term follow-up; lt, long-term follow-up.

Salivary flow, frequency, and severity

Salivary flow, frequency, and severity include ingestion functions (b510). BoNT-A compared with scopolamine may reduce salivary flow at the 0 to 2, 4, and 8-week follow-ups; however, it may make little to no difference at 16 and 24 weeks (low certainty evidence).[28] Moreover, BoNT-A may reduce the frequency and severity of drooling at 4 and 16 weeks, while no effect was observed for both treatments at 24 weeks. Scopolamine may not reduce drooling at 2 weeks from baseline (low certainty evidence).[28]

When compared with placebo, BoNT-A may reduce salivary flow at 6 and 12 weeks; however, it may make no difference compared to baseline and at 0 to 2, 4, 8, 10, 14, 18, and 22 weeks (low certainty evidence).[28] When assessed with the Drooling Quotient, BoNT-A, compared with placebo, may decrease the frequency and severity of drooling at 0 to 2, 4, 6, 8, and 12 weeks; however, it may make little to no difference at 10, 14, 18, and 22 weeks after injection (low certainty evidence).[28]

Compared to placebo, benztropine and glycopyrrolate may reduce the frequency and severity of salivary flow (low certainty evidence).[28]

Spasticity and dystonia

Spasticity and dystonia include muscle tone functions (b735) and range of motion (mobility of joint functions [b710]). Compared to usual care or physiotherapy, it is uncertain if BoNT-A improves ankle plantar flexor spasticity and ankle range of motion (very low certainty evidence).[33]

Compared to serial casting, BoNT-A may make no difference in improving ankle plantar flexor spasticity and ankle range of motion at any point (low certainty evidence).[33] It is uncertain whether BoNT-A improves hip range of motion

and hip adductors spasticity compared to Johnstone pressure splints (very low certainty evidence).[33]

In the dystonic form of CP, trihexyphenidyl may make a minimal difference compared with placebo on change in dystonia from baseline; however, the risk of adverse effects may be higher with trihexyphenidyl (low certainty evidence).[31]

Activity and participation

This category includes activity and participation in activities of daily living, self-care, and occupational performance, including performance and satisfaction (i.e. carrying out daily routine, [d230], hand and arm use [d445], caring for body parts [d520], basic interpersonal interactions [d710], school education [d820], community life [d910], recreation and leisure [d920]).

Compared to usual care, resistance training may have no effect on participation in activities of daily living (low certainty evidence).[30]

Compared to dose-matched treatments, CIMT may have no effect on self-care, while its effect on overall performance is uncertain (very low certainty evidence).[32]

Trihexyphenidyl compared with placebo may improve performance and participation in activities of daily living in children with dystonic CP (low certainty evidence).[31]

No difference was found in terms of participation and quality of life when comparing mechanically assisted walking training with body weight support to the same dose of overground walking training (low certainty evidence).[34]

Gross motor function

Gross motor function includes walking (d450) and moving around (d455). Compared with usual care, aerobic exercise may improve gross motor function (low certainty evidence); its effect on gait speed is uncertain (very low certainty evidence).[30] Resistance training may have no effect on gross motor function and gait speed in the short (0–1 month) and intermediate term (1–6 months). Mixed training may have no effect on gross motor function compared with usual care. Resistance training has no effect on gross motor function when compared with aerobic exercise (both comparisons, low certainty evidence).[30]

The effect of BoNT-A on mobility is uncertain when compared to orthoses or usual care or physiotherapy (very low certainty evidence).[33]

Compared with no walking training, mechanically assisted walking training without body weight support may improve gross motor function (low certainty evidence).[34] There is no difference in gross motor function outcomes between mechanically assisted walking training with body weight support and no walking training or the same dose of overground walking training (low certainty evidence).[34]

Bimanual performance and unimanual capacity

Bimanual performance and unimanual capacity include hand and arm use (d445) and fine hand use (d440). Compared with low-dose therapy (total hours of intervention ranged from 0 to 25 hours), CIMT may improve bimanual performance (low certainty evidence); its effect on unimanual capacity is uncertain (very low certainty evidence).[32] When compared to high-dose therapy (>25 hours of intervention but less than the experimental group), CIMT may have no effect on bimanual and overall performance (low certainty evidence). The effects on unimanual capacity and self-care are uncertain (very low certainty evidence).[32]

Compared to dose-matched treatments (experimental and comparison groups received equal dosages of therapist-led, parent-led, and other interventions), CIMT may have no effect on bimanual performance and unimanual capacity when measured with the Melbourne Assessment scale (low certainty evidence).[32] The effects on unimanual capacity, when measured with the Quality of Upper Extremity Skills Test, are unclear (very low certainty evidence). It is uncertain whether CIMT compared to different forms of CIMT has an effect on bimanual performance and unimanual capacity (very low certainty evidence).[32]

Gait scores

Gait scores include walking (d450). It is uncertain whether BoNT-A improves overall gait scores at any follow-up interval (observational gait analysis) compared to usual care or physiotherapy (very low certainty evidence).[33]

Compared to the same dose of overground walking training, mechanically assisted walking training with body weight support may make no difference to walking speed (low certainty evidence).[34]

DISCUSSION

Our study addressed a mapping synthesis of current evidence on the effectiveness of rehabilitation interventions for individuals with CP.

Our findings show that BoNT-A injection is a possible pharmacological approach for managing upper-limb spasticity, satisfaction, performance, activity-level goal attainment, and quality of movement in individuals with CP. In particular, when BoNT-A injection is used in addition to occupational therapy, it improves wrist and elbow flexor spasticity at 3 months after treatment more than when it is applied alone. However, there is uncertainty about whether occupational therapy enhances the effects of BoNT-A injection on satisfaction, performance, quality of movement, and elbow spasticity and whether high-dose BoNT-A improves upper-limb spasticity.

On the other hand, BoNT-A alone probably improves function and ankle plantar flexor spasticity at 8 weeks after the treatment.

Non-pharmacological treatments, such as mechanically assisted walking without body weight support, probably improve gait, gross motor function, and participation, and CIMT may improve bimanual performance and unimanual capacity. There is uncertainty on the effect of a sleep-positioning system on sleep patterns, child and family quality of life, pain, and physical functioning.

Our findings support the guidelines of the National Institute for Health and Care Excellence, which encourage a multimodal approach that includes BoNT-A combined with other non-pharmacological treatments because it may be more effective in the treatment of CP-associated conditions.[36] Some studies report that BoNT-A associated with regular physiotherapy, muscle stretching, adhesive taping, and serial casting may reduce upper- and lower-limb spasticity.[37,38] Indeed, children with CP presenting with spastic wrist flexion deformity might gain additional benefits from supplementary intermittent serial casting as well as from BoNT-A injections and occupational therapy.[39]

Despite these promising findings, we need to consider two important aspects of this approach: safety and costs. A recent study suggests caution in BoNT-A administration because, apart from its therapeutic effect in spasticity reduction, it might cause muscle atrophy and some other adverse events that may not completely reversible.[40] Regarding the second aspect, the use of BoNT-A and mechanically assisted walking are associated with cost-related barriers and must be administered by a trained professional. In high-income countries, these treatment options are commonly available in locations with a high population density, but more remote areas may suffer from a lack of services and adequate transport, inevitably leading to access issues. In LMICs, these treatments are not readily available[41] and people with CP continue to experience more severe motor impairments, lower quality of life, and higher mortality rates.[42] While physiotherapy interventions may be less costly and safer than other interventions, such as BoNT-A, the uncertainty of their effectiveness, the lack of early diagnostic and rehabilitation services, and the low awareness by caregivers of the services needed for children with CP contribute to disparities in service availability, use, and treatment outcomes in some countries.[41]

Furthermore, the guidelines do not give specific recommendations and highlight the need for more research on low-cost, impairment-based interventions specifically targeting these areas.[43–45] Therefore, our findings could drive future research to investigate the most appropriate post-BoNT-A injection treatment based on a multimodal approach to optimize a personalized treatment and encourage favourable outcomes.

Considering the complexity of children with CP and their rehabilitative needs, further studies are needed to investigate the effectiveness of different rehabilitation interventions. To improve the quality of evidence, primary studies of higher quality are needed, using more sophisticated statistical analysis, such as subgroup analysis, and efforts should be made to identify rehabilitation interventions for CP that are equally effective and efficient in diverse cultural and economic settings to promote equitable clinical outcomes and services.

Strengths and limitations

This overview has contributed to making the most relevant evidence on rehabilitation interventions for individuals with CP more digestible and accessible for the community. All CSRs were evaluated using the GRADE approach and the broad global representation from the included trials (i.e. the UK, Saudi Arabia, Greece, Republic of Korea, India, South Africa, Egypt, Taiwan, and the USA)[27–34] bolsters the reproducibility of the results in different countries and settings. However, all included CSRs did not consider other types of rehabilitation interventions, such as the use of technology, approaches to vision impairments, and improvement in functional outcomes, and there were no studies that considered adults. Our findings resulted from the selection of CSRs according to the methods framed by the WHO Rehabilitation Programme and Cochrane Rehabilitation. We exclusively included CSRs because they represent the criterion standard among systematic reviews because of the high-quality of their methodology; this could limit the generalizability of the findings and investigated interventions.[46] However, the uniformity of the Cochrane methodology gives coherence to the overview and is currently suggested by the WHO. Not providing a full evidence map that should start from an a priori grid developed according to a specific methodology, including all the possible outcomes and interventions, is another limitation. Moreover, according to the reported interventions and outcomes, we provided only the GRADE evidence of the current CSRs. Although beyond the scope of this paper, the authors acknowledge that this did not allow the full identification of evidence gaps.

Conclusions

This overview provides the current, most reliable evidence on rehabilitation interventions in individuals with CP according to the methods outlined by the WHO Rehabilitation Programme and Cochrane Rehabilitation. The findings support the role of BoNT-A combined with other non-pharmacological treatments in the management of spasticity and reveal a paucity of randomized controlled trials examining both pharmacological and non-pharmacological treatments for dystonia and postural deformities. Studies with larger sample sizes and rigorous methodology should further investigate the effectiveness of rehabilitation interventions for the management of CP, including safety and economic outcomes.

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DATA AVAILABILITY STATEMENT

Data will be available upon reasonable request.

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SUPPORTING INFORMATION

The following additional material may be found online:
Table S1: Characteristics of the CSRs included.

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