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Efficacy of Upper Limb Therapies for Unilateral Cerebral Palsy: A Meta-analysis

AUTHORS: Leanne Sakzewski, PhD, BOccThy,[a,b] Jenny Ziviani, PhD, MEd, BA, BAppScOT,[b,c] and Roslyn N. Boyd, PhD, MSc (Physiotherapy)[a,b]

[a]Queensland Cerebral Palsy and Rehabilitation Research Centre, School of Medicine, and [c]School of Health and Rehabilitation Sciences, Faculty of Health Sciences, The University of Queensland, Brisbane, Australia; and [b]Queensland Medical Research Institute, Brisbane, Australia

KEY WORDS
cerebral palsy, upper limb rehabilitation, systematic review, meta-analysis, botulinum toxin A, constraint-induced movement therapy

ABBREVIATIONS
AHA—Assisting Hand Assessment
BoNT-A—botulinum toxin A
CI—confidence interval
cCIMT—classic constraint-induced movement therapy
CIMT—constraint-induced movement therapy
COPM—Canadian Occupational Performance Measure
CP—cerebral palsy
ES—effect size
HABIT—hand arm bimanual intensive training
mCIMT—modified constraint-induced movement therapy
NDT—neurodevelopmental treatment
OT—occupational therapy
PEDro—Physiotherapy Evidence Database
PMAL—Pediatric Motor Activity Log
QUEST—Quality of Upper Extremity Skills Test
RCT—randomized controlled trial
SMD—standardized mean difference
UL—upper limb

Dr Sakzewski conceptualized and designed the review protocol, performed the initial database searches, rated the quality of included trials and extracted data and performed all statistical analyses, and drafted the initial manuscript; Dr Ziviani assisted with the quality ratings of included reviews and reviewed and revised the manuscript; Dr Boyd conceptualized and reviewed the protocol and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

(Continued on last page)

abstract

FREE

BACKGROUND AND OBJECTIVE: Children with unilateral cerebral palsy present with impaired upper limb (UL) function affecting independence, participation, and quality of life and require effective rehabilitation. This study aims to systematically review the efficacy of nonsurgical upper limb therapies for children with unilateral cerebral palsy.

METHODS: Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Embase, the Cochrane Central Register of Controlled Trials, and PubMed were searched to December 2012. Randomized controlled or comparison trials were included.

RESULTS: Forty-two studies evaluating 113 UL therapy approaches (N = 1454 subjects) met the inclusion criteria. Moderate to strong effects favoring intramuscular injections of botulinum toxin A and occupational therapy (OT) to improve UL and individualized outcomes compared with OT alone were identified. Constraint-induced movement therapy achieved modest to strong treatment effects on improving movement quality and efficiency of the impaired UL compared with usual care. There were weak treatment effects for most outcomes when constraint therapy was compared with an equal dose (amount) of bimanual OT; both yielded similar improved outcomes. Newer interventions such as action observation training and mirror therapy should be viewed as experimental.

CONCLUSIONS: There is modest evidence that intensive activity-based, goal-directed interventions (eg, constraint-induced movement therapy, bimanual training) are more effective than standard care in improving UL and individualized outcomes. There is little evidence to support block therapy alone as the dose of intervention is unlikely to be sufficient to lead to sustained changes in UL outcomes. There is strong evidence that goal-directed OT home programs are effective and could supplement hands-on direct therapy to achieve increased dose of intervention. *Pediatrics* 2014;133:e175–e204

Congenital hemiplegia, the most common form of cerebral palsy (CP), accounts for 1 in 1300 live births.[1] For children with unilateral CP, the effect on upper limb (UL) function is often more pronounced than that on lower limb function,[2] with resultant limitations in daily independence, participation, and quality of life. Rehabilitation addressing UL dysfunction is paramount to promote better use of the impaired arm and hand in day-to-day bimanual activities and to achieve functional independence in home, school, and community endeavors.

A number of UL rehabilitation approaches have been reported in children with unilateral CP. Our previous systematic review and meta-analysis identified 12 randomized controlled trials (RCTs) of constraint-induced movement therapy (CIMT), hand arm intensive bimanual training (HABIT), neurodevelopmental treatment (NDT), and intramuscular injections of botulinum toxin A (BoNT-A) augmenting occupational therapy (OT).[3] Findings suggested that intramuscular injections of BoNT-A provided a modest supplementary effect to OT on improving UL outcomes and a strong effect on improving individualized goals. The limited studies of NDT indicated weak to moderate effects on improving quality of UL movement and fine motor skills, despite being commonly used in clinical practice.[4,5] The small number of trials of CIMT and HABIT at the time, and lack of uniform outcome measures, limited pooling of data across trials. Individually, there appeared to be promising results suggesting that these 2 high-intensity therapies might yield significant gains in UL function. Adequately powered RCTs of CIMT and HABIT using reliable and valid outcome measures were recommended.[3]

In the past 4 years, a large number of RCTs particularly investigating CIMT and modified CIMT (mCIMT) have emerged. Classic CIMT (cCIMT), described in earlier studies, involved placing a full arm cast on the unimpaired UL for 21 consecutive days, accompanied by intensive training for 6 hours each day.[6] Modifications to the classic protocol (mCIMT) have been made to make it more child-friendly.[7] mCIMT protocols similarly involve restraint of the unimpaired UL, with variations in the type of restraint applied (eg, glove, mitt, sling), and are accompanied by repetitive unimanual task practice. mCIMT departs from cCIMT in terms of the model of therapy delivery (intensive short duration, longer duration distributed model) and dose of intervention. Recently, hybrid models sequentially applying mCIMT followed by bimanual training have been reported.[8,9] As a result of the increase in RCTs of UL therapies, conclusions of our previous systematic review need updating. The aim of this systematic review was to determine the efficacy of all nonsurgical UL therapies for children and youth (aged 0–18 years) with unilateral CP on UL outcomes, achievement of individualized goals, and self-care skills.

METHODS

Search Strategy

Five databases were searched from inception to December 2012 (Medline, CINAHL [Cumulative Index to Nursing and Allied Health Literature], Embase, PubMed, and the Cochrane Central Register of Controlled Trials). Exploded Medical Subject Heading (MeSH) terms and key words used were as follows: (1) cerebral palsy OR hemipleg*, AND (2) child OR infant OR adolescent, AND (3) physical therapy/physiotherapy OR occupational therapy OR neurodevelopmental therapy/bobath OR functional therapy OR motor learning OR splints OR casts, surgical or botulinum toxin A/neurotoxin OR functional electrical stimulation/neuromuscular electrical stimulation OR resistance training/strength* OR conductive education OR virtual reality OR constraint induced movement therapy OR bimanual training OR action observation OR mirror therapy, AND (4) UL OR upper extremity OR arm OR hand, AND (5) randomized controlled trial/randomized trial OR random sampling OR double-blind method OR single blind method OR placebo. Additional hand searching of reference lists was performed. A language restriction to publications in English was included due to lack of translation services.

Inclusion Criteria

Eligibility for inclusion, based on title and abstract, was assessed independently by 2 reviewers (L.S. and R.N.B.). Abstracts meeting inclusion criteria or requiring more information from the full text to clarify inclusion were retained. Articles were included when 100% agreement between reviewers was achieved. Inclusion criteria were as follows: (1) study was an RCT, (2) population comprised children 0 to 18 years of age with unilateral CP, (3) study evaluated the efficacy of a nonsurgical UL therapy or adjunctive treatment in combination with UL therapy, (4) outcomes measured UL unimanual or bimanual capacity and performance, achievement of individualized goals, or self-care skills. Articles were excluded if they used quasi-randomization methods, did not include a subset of children with unilateral CP, provided general developmental therapy without specified UL training, or outcomes assessed impairment, quality of life, or participation.

Data Extraction, Quality Assessment, and Analyses

Structured data extraction forms were developed. For studies that did not have the required data published, authors were contacted to request relevant information. Study methodology, number of participants, and intervention and

control group details were summarized (Table 1). The methodologic quality of included studies was rated independently by 2 reviewers (L.S. and R.F.) by using the Physiotherapy Evidence Database (PEDro) scale.[10] Ten criteria were each scored as either 0 or 1, with a possible total score of 10. Disagreements were resolved by a third reviewer (J.Z.).

Data management and analyses were performed by using RevMan 5.1 (Cochrane Collaboration, Oxford, England). Continuous outcomes for each study were summarized by using means, effect sizes (ESs), and 95% confidence intervals (CIs). An ES of 0.2 was considered small, 0.4 to 0.6 moderate, and 0.8 large. For meta-analyses, standardized mean differences (SMDs) and 95% CIs were calculated. Pooled treatment effects were calculated across trials by using a fixed-effects model when trials used similar interventions and outcomes on similar populations. When substantial heterogeneity between studies was evident from the I^2 statistic, a random-effects model was used.[11] Data partly or in whole duplicated in a number of publications were scrutinized, and only the most complete data set was included. Outcomes with inadequate reported validity and/or reliability were excluded from meta-analysis.

RESULTS

Description of Studies

A total of 302 unique references were identified, and 55 full-text articles retrieved for full appraisal. Forty-nine publications reporting 42 trials were included (Fig 1). Study characteristics and methods of included RCTs are summarized in Table 1.

Thirteen types of UL interventions and numbers of participants were identified: NDT (2 studies; n = 122),[12,13] intramuscular injections of BoNT-A and OT (11 studies; n = 322),[14–24] cCIMT (3 studies; n = 56),[6,25–28] mCIMT (15 studies; n = 578),[7,29–47] hybrid model (mCIMT and bimanual training; 2 studies; n = 68),[8,9] forced-use therapy (2 studies; n = 54),[48,49] HABIT (1 study; n = 20),[50] OT home programs (1 study; n = 35),[51] UL lycra splints (1 study; n = 16),[52] context-focused therapy (1 study; n = 128),[53] mirror box therapy (1 study; n = 10),[54] acupuncture combined with OT (1 study; n = 75),[55] and action observation training (1 study; n = 15).[56] A number of studies reported different domains of outcome (eg, activity, participation)[25,33,36] or different times for follow-up[34,39,43] in separate papers. Details of each intervention and duration, frequency, and intensity of intervention for control and comparison groups are summarized in Table 2.

Age of participants across trials ranged from 7 months to 16 years; the majority were preschool- to school-aged children. One study reported outcomes for infants <1 year of age,[6] and 10 studies reported on children <2 years of age.[12,13,20,29,30,37,40,47,53,55] Most studies targeted children with unilateral CP, and 13 included children with other subtypes of CP (eg, quadriplegia).

Overall dose, frequency, intensity, and duration of therapy varied across studies. OT after UL injections of BoNT-A ranged from 1 session per fortnight[14] to 3 times per week[15,24] for a minimum of 4 weeks[19] to a maximum of 6 months.[15,24] Home programs were provided in 4 studies, with minimal detail.[16,17,20,22] Total doses of therapy ranged from 4 to 78 hours.[15,19,24] Higher intensities and dosage of intervention were reported in studies of cCIMT, mCIMT, HABIT, and hybrid therapy. Short-duration, high-intensity programs ranged from 2 to 3 weeks' duration providing 6 hours of daily therapy, with totals of 60 to 126 hours.[6,26,27,50] Less-intensive, longer-duration models delivered intervention over 4 to 10 weeks, ranging from 1 to 3 sessions per week, 1 to 4 hours per session.[8,29–31,37,38,40,42,44–47] These models often relied on caregivers to provide varying amounts of home practice to achieve the required dosage of intervention, with the expected total ranging from 15 to 168 hours.[31,37,40,42,44,47] Studies delivered intervention in context at home/preschool,[26,31,37,40,43,44] in a clinic,[6–8,35,41,50] or in the community.[32]

Qualitative Assessment

Quality ratings of the study design are reported in Table 3. Twelve studies were of very high methodologic quality, scoring ≥8 on the PEDro scale.[10] Fourteen studies were of poor methodologic quality, scoring <6 on the PEDro scale (BoNT-A,[21–23] cCIMT,[6,25,26] mCIMT,[7,29,30,38,44] forced-use therapy,[48] and other UL interventions[50,54,56]). Twenty-six studies (57%) did not report concealed allocation. Baseline equivalence between groups was not present in 12 studies (26%). Data from 6 studies (9 publications) were not included in meta-analyses. One study reported median scores,[15] 6 did not present summary statistics of central tendency and variability,[21,22,25,28,38,56] and 2 reported change scores with or without SDs.[41,55]

For quantitative comparison of outcomes, data were available to pool across trials and 2 main comparisons were performed: (1) BoNT-A and OT versus OT alone and (2) cCIMT or mCIMT versus (a) a control group or therapy group receiving a lesser dosage of therapy or (b) a comparison group receiving an equivalent dosage of an alternative intervention.

Primary Outcomes: Unimanual and Bimanual UL Function

Results of studies reporting UL outcomes are summarized in Table 4. All meta-analyses are summarized in Table 5 and depicted in forest plots in Figs 2 and 3. Data from 4 studies of BoNT-A and OT (n = 55) compared with

TABLE 1 Study Characteristics and Methods of RCTs of Nonsurgical Interventions in Children With Congenital Hemiplegia

Study Grouped by Intervention	Design	Diagnosis	Age	Treatment	*n*	Control	*n*
NDT							
Law et al (a)[12]	RCT	CP	18 mo to 8 y	Intense NDT and casting	19	Intensive NDT	18
Law et al (b)[12]				Regular NDT and casting	17	Regular NDT	18
Law et al (a)[13]	RCT cross-over	CP	18 mo to 4 y	Intense NDT and casting first	26	Regular OT	24
Law et al (b)[13]				Intense NDT and casting second	26	Regular OT	24
BoNT-A							
Fehlings et al[14]	SB RCT	Hemi CP	2 to 10 y	BoNT-A and OT	14	OT	15
Speth et al[15]	Matched-pairs RCT	Hemi CP	4 to 16 y	BoNT-A and OT/PT	10	OT/PT	10
Lowe et al[16]	SB RCT	Hemi CP	2 to 8 y	BoNT-A and OT	21	OT	21
Kawamura et al[17]	DB RCT	CP	30 mo to 12 y	Low-dose BoNT-A and OT	18	High-dose BoNT-A and OT	21
Wallen et al (a)[18]	SB RCT	CP	2 to 14 y	BoNT-A	19	Control	15
Wallen et al (b)[18]	SB RCT	CP	2 to 14 y	BoNT-A and OT	20	OT	17
Russo et al[19]	SB RCT	Hemi CP	3 to16 y	BoNT-A and OT	21	OT	22
Olesch et al[20]	SB RCT	Hemi CP	18 mo to 5 y	Repeat BoNT-A and OT (3 injections)	11	OT	11
Kanellopoulos et al[21]	RCT	Hemi CP	2.5 to 12 y	BoNT-A, OT and night splint	10	BoNT-A and OT	10
Rameckers et al[24]	Matched-pairs SB RCT	Hemi CP	4 to16 y	BoNT-A and task-oriented training	10	Task-oriented training	10
Pieber et al[22]	SB RCT	Hemi CP	7 to 17 y	FES, OT, and BoNT-A	3	BoNT-A and OT	3
Elvrum et al[23]	SB RCT	CP	9 to 17 y	BoNT-A and resistance training	5	BoNT-A	5
cCIMT							
Taub et al[6]	RCT	CP	7 mo to 8 y	CIMT	9	Regular therapy	9
Deluca et al[25]	SB RCT cross-over	CP	7 mo to 8 y	CIMT	9	Control	9
				CIMT second		Control	
Taub et al[26]	RCT cross-over	Hemi CP	2 to 6 y	CIMT first	10	Usual care	10
				CIMT second	10	Usual care	10
Case-Smith et al[27] and Deluca et al[28]	SB RCT	Hemi CP	3 to 6 y	CIMT (3 h/d)	9	CIMT (6 h/d)	9
mCIMT							
Charles et al[7]	SB RCT	Hemi CP	4 to 8 y	mCIMT	11	Control	11
Smania et al[29]	RCT cross-over	Hemi CP	1 to 9 y	mCIMT first	5	PT	5
				mCIMT second		PT	
Al-Oraibi et al[30]	SB RCT	Hemi CP	22 to 105 mo	mCIMT	7	NDT	7
Lin et al[31]	SB RCT	CP	4 to 9 y	mCIMT	10	Therapy	11
Sakzewski et al[32]	SB RCT	Hemi CP	5 to 16 y	mCIMT	32	BIM training	31
Wallen et al[37]	SB RCT	Hemi CP	19 mo to 7 y	mCIMT	25	Standard OT	25
Gordon et al[58]	SB RCT	Hemi CP	3 to 10 y	mCIMT	21	HABIT	21
Facchin et al[38] and Fedrizzi et al[39]	Cluster RCT	Hemi CP	2 to 8 y	mCIMT	39	BIM training	33
				mCIMT	39	Standard care	33
				BIM training	33	Standard care	33
Eliasson et al[40]	SB RCT cross-over	Hemi CP	1.5 to 5 y	Eco mCIMT first	12	Usual care	13
				Eco mCIMT second	13	Usual care	12
Xu et al (a)[41]	SB RCT	Hemi CP	2 to 14 y	mCIMT and FES	22	mCIMT	23
Xu et al (b)[41]	SB RCT	Hemi CP	2 to 14 y	mCIMT	23	OT	23
Hsin et al[42]	SB RCT	Hemi CP	6 to 8 y	mCIMT (home)	11	Standard care	11
Chen et al[43]	SB RCT	Hemi CP	6 to 12 y	mCIMT (home)	24	Standard care	23
Rostami et al (a)[44]	SB RCT	Hemi CP	74 mo (mean)	mCIMT (home)	7	mCIMT (clinic)	7
Rostami et al (b)[45]	SB RCT	Hemi CP	6 to 11 y	mCIMT	8	mCIMT and VR	8
Rostami et al (c)[45]	SB RCT	Hemi CP	6 to 11 y	mCIMT	8	Control	8
Choudhary et al[46]	SB RCT	Hemi CP	3 to 8 y	mCIMT	16	Regular therapy	15
Hoare et al[47]	SB RCT	Hemi CP	18 mo to 6 y	BoNT-A and CIMT	17	BoNT-A and BIM OT	17
Hybrid model: combined mCIMT and bimanual training							
de Brito Brandão et al[9]	SB RCT	Hemi CP	4 to 8 y	mCIMT and BIM	8	Regular therapy	8
Aarts et al[8]	SB RCT	Hemi CP	30 mo to 8 y	mCIMT-BiT	28	Regular therapy	24

TABLE 1 Continued

Study Grouped by Intervention	Design	Diagnosis	Age	Treatment	*n*	Control	*n*
Forced-use therapy							
Sung et al[48]	RCT	Hemi CP	≤8 y	Forced-use and regular therapy	18	Regular therapy	13
Eugster-Buesch et al[49]	SB RCT	Hemi CP	6 to 16 y	Forced use	12	Control	11
Other UL interventions							
Gordon et al[50]	SB RCT	Hemi CP	3 to 15 y	HABIT	10	Control	10
Novak et al (a)[51]	DB RCT	CP	4 to 12 y	OT home program (8 wk)	12	No OT home program	12
Novak et al (b)[51]	DB RCT	CP	4 to 12 y	OT home program (4 wk)	11	No OT home program	12
Elliott et al[52]	RCT	CP	8 to 15 y	Lycra splint and goal-directed training	8	Goal-directed training	8
Gygax et al[54]	SB RCT cross-over	Hemi CP	6 to 14 y	Mirror therapy: BIM with mirror first	5	BIM without mirror	5
				BIM without mirror first	5	BIM with mirror second	5
Law et al[53]	SB cluster RCT	CP	1 to 5 y	Child focused	71	Context focused	57
Duncan et al[55]	SB RCT	CP	12 to 72 mo	Intensive therapy and acupuncture	46	Intensive therapy	29
Buccino et al[56]	DB RCT	CP	6 to 11 y	Action observation	8	Control	7
Rostami et al (d)[45]	SB RCT	Hemi CP	6 to 11 y	VR	8	Control	8

BIM, bimanual training; BiT, bimanual therapy; DB, double-blind; Eco, ecological; Hemi, hemiplegia; FES, functional electrical stimulation; PT, physiotherapy; SB, single blind; VR, virtual reality.

OT alone ($n = 53$) scored an SMD of 0.35 (95% CI: −0.03 to 0.73; $P = .07$) for quality of UL movement on the Quality of Upper Extremity Skills Test (QUEST). This difference was not sustained at 6 to 8 months postintervention. QUEST scores on the Grasp Domain were pooled for 3 studies comparing mCIMT ($n = 72$) with a control group ($n = 65$) and yielded an SMD of 0.30 (95% CI: −0.04 to 0.64; $P = .08$). When mCIMT ($n = 60$) was compared with a group receiving an equal dose of an alternate intervention ($n = 54$), the effect on the QUEST Grasp Domain was an SMD of 0.11 (95% CI: −0.26 to 0.47; $P = .57$). Movement efficiency measured on the Bruininks-Oseretsky Test of Motor Proficiency subtest 8 achieved a strong treatment effect favoring mCIMT compared with a control group (SMD: 1.95; 95% CI: −1.01 to 4.95; $P = .20$) and compared with an equal-dose comparator (SMD: 0.82; 95% CI: 0.12 to 1.52; $P = .02$). There was a negligible effect of mCIMT compared with an equal dose of bimanual training on bimanual outcomes measured on the Assisting Hand Assessment (AHA) (SMD: −0.04; 95% CI: −0.42 to 0.35; $P = .86$) and a weak effect when compared with a control group (SMD: 0.13; 95% CI: −0.39 to 0.66; $P = .62$).

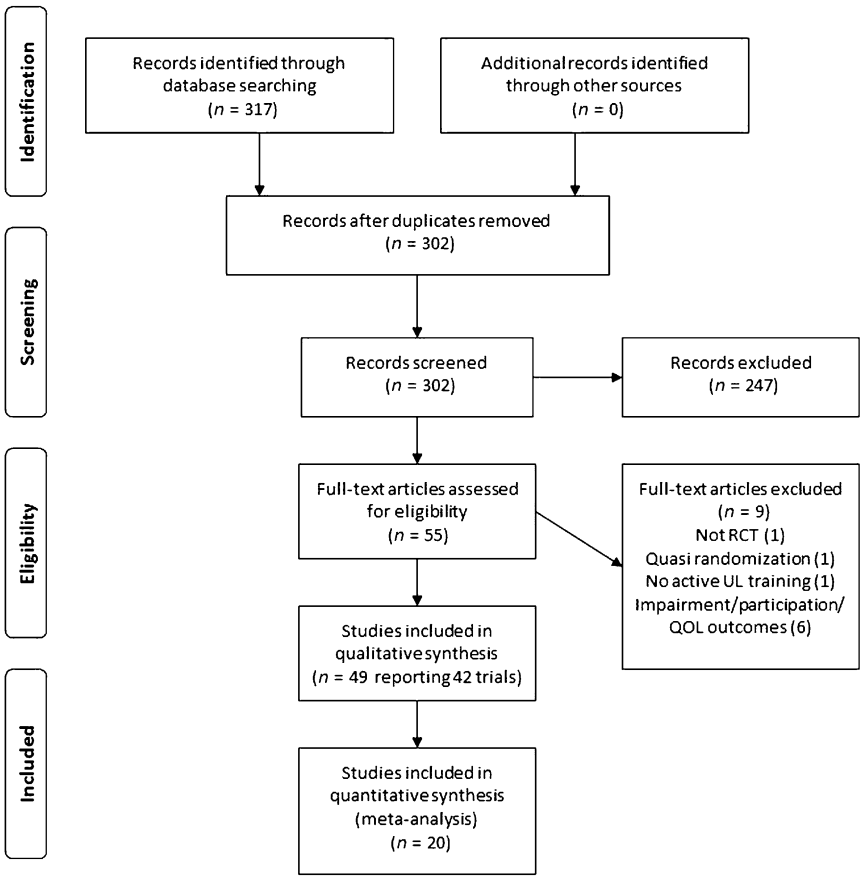


FIGURE 1
Results of search strategy of UL systematic review. QOL, quality of life.

Achievement of Individualized Goals

Results of studies reporting individualized outcomes are summarized in Table 6. Canadian Occupational Performance Measure (COPM) performance scores were pooled from 3 studies comparing BoNT-A and OT ($n = 55$) with

TABLE 2 Structure and Content of Nonsurgical UL Intervention Programs for Children With Congenital Hemiplegia

Study	Content of Intervention Program	Duration, wk	Frequency of Sessions	Intensity	Home Program	Content of Control Group	Duration, wk	Frequency of Sessions	Intensity	Home Program
NDT										
Law et al (a)[12]	Intensive NDT: bivalved cast	26	2/wk 7/wk	0.75 h 4 h	0.5 h/d	Intensive NDT only	26	2/wk	0.75 h	0.5 h/d
Law et al (b)[12]	Regular NDT: bivalved cast	26	1/wk (maximum) to 1/mo (minimum)	0.75 h 4 h/d	0.25 h/d (3 d/wk)	Regular NDT only	26	1/wk (maximum) to 1/mo (minimum)	0.75 h	0.25 h (3d/wk)
Law et al (a)[13]	NDT: bivalved cast	16	2/wk (minimum)	0.75 h 4 h/d	0.5 h/d	Regular OT-functional skills	16	1/wk (maximum) to 1/mo (minimum)	0.75 h	Previous therapy
Law et al (b)[13]	NDT and casting second	16	a/a	a/a	a/a	Regular OT (a/a)	16	a/a	a/a	a/a
BoNT-A										
Fehlings et al[14]	Botox injections: dose, 2–6 U/kg; therapy: strength, ADLs	26	0.5/wk	NR	NR	OT (as per intervention group)	26	0.5/wk	NR	NR
Speth et al[15]	Botox injections: dilution, 5 U/0.1 mL; maximum dose, 400 U/kg; OT: strength, functional training, orthoses	26	3/wk each OT and PT	OT: 0.5 h PT: 0.5 h	NR	OT (as per intervention group)	26	3/wk	OT–0.5 h PT–0.5 h	NR
Lowe et al[16]	Botox injections: dilution, 100 U/0.5 mL; maximum dose, <8 U/kg; total dose, 82–220 U; therapy: goal-directed, splint, strength	26	OT NR	NR	Reported without detail	OT (as per intervention group)	26	NR	NR	Reported without detail
Kawamura et al[17]	Low-dose Botox injections: dilution, 100 U/1.0 to 2.0 mL; therapy: community-based, goal-directed, strength, fine motor, and ADLs	12	0.7/wk	NR	6 wk (reported without detail)	High-dose Botox injections: dilution 100 U/0.5–1.0 mL; therapy: as per low-dose group	12	0.5/wk	NR	5.3 wks (reported without detail)
Wallen et al (a)[18]	Botox injections: dose, 0.5–2 U/kg; maximum dose, 12 U/kg: regular therapy	26	Maintained previous level	Maintained previous level	NR	Control group	26	Maintained previous level		NR
Wallen et al (b)[18]	Botox injections: dose, 0.5–2 U/kg; maximum dose, 12 U/kg; therapy: stretch, cast, motor training, goal-directed	12	1/wk	1 h	NR	OT as described for intervention group	12	1/wk	1 h	NR

TABLE 2 Continued

Study	Content of Intervention Program	Duration, wk	Frequency of Sessions	Intensity	Home Program	Content of Control Group	Duration, wk	Frequency of Sessions	Intensity	Home Program
Russo et al[19]	Botox injections: dilution, 100 U/mL; maximum dose, <12 U/kg; total dose, 300 U; therapy: wt bearing, ball skills, strength, goal-directed	4	1/wk	1 h	NR	OT as described for intervention group	4	1/wk	1 h	NR
Olesch et al[20]	Botox injections: 3 series in 16-wk cycles; dilution, 100 U/mL; therapy: goal-directed	6 each cycle	2/wk	NR	Program but no detail provided	OT	6 each cycle	2/wk	NR	Program but no detail provided
Kanellopoulos et al[21]	Botox injections: therapy, detail not reported; themoplastic night splint	26	3/wk	NR	NR	Botox injections and OT	26	3/wk	NR	NR
Rameckers et al[24]	Botox injections: dilution, 5 U/0.1 mL; maximum dose, 400 U; OT/PT: strength, task-specific training; night splint; daytime wrist splint for children Zancolli IIB	26	3/wk	0.5 h OT 0.5 h PT	NR	PT/OT: strength, task-specific training; night splint; daytime wrist splint for children Zancolli IIB	26	3/wk	0.5 h OT 0.5 h PT	NR
Pieber et al[22]	Botox injections: maximum dose, 12 U/kg; total dose, 300 U; FES: 30 Hz, 0.2-ms pulse width, 2–5 s on time, 2–5 s off time; night splint	6	1/wk (OT/PT)	0.5 h OT 0.5 h PT	0.5 h (FES) 5 times/wk	Botox injections and OT, night splint	6	1/wk	0.5 h OT 0.5 h PT	NR
Elvrum et al[23]	Botox injections: dilution, 100 U/mL; resistance training, core strengthening, single joint 3 sets of 10 repetitions, progressive increase of 0.25–0.5 kg	8	3/wk	0.8 h	NR	Botox injections	8	NR	NR	NR
cCIMT										
Taub et al[6] and Deluca et al[25]	Restraint: long arm bivalve cast; context: individual clinic-based; training: repetitive task practice, shaping reach, grasp, wt bearing, manipulate, ADLs	3	7/wk	6 h	NR	Standard OT/PT	3	1 session/wk (minimum) to 4 sessions/wk (maximum)	2.2 h/wk (mean)	NR

TABLE 2 Continued

Study	Content of Intervention Program	Duration, wk	Frequency of Sessions	Intensity	Home Program	Content of Control Group	Duration, wk	Frequency of Sessions	Intensity	Home Program
Taub et al[26]	Restraint: long arm cast; 13 d cCIMT, 2 d BIM; context: home-based; training: repetitive task practice, shaping in play, and ADLs	2.1	7/wk	6 h	NR	Usual care	2.1	1/wk	1–2 h	NR
Case-Smith et al[27] and DeLuca et al[28]	Restraint: full arm cast; training: 18 d cCIMT, 3 d BIM	3	5/wk	6 h	NR	CIMT: Restraint: full arm cast; training: 18 d CIMT, 3 d BIM	3	5/wk	3 h	NR
mCIMT										
Charles et al[7]	Restraint: sling; context: clinic-based groups of 2 to 4; training: movement training, play, functional therapy	2	5/wk	6 h	1 h/d for CIMT 2 h/d (for 6 mo post CIMT	Maintained previous levels	2	NR	NR	NR
Smania et al[29]	Restraint: mitt; context: individual; training: repetitive practice, play	5	2/wk	1 h	Mitt worn 8 h/d	PT	5	2/wk	1 h	NR
Al Oraibi et al[30]	Restraint: glove; context: home- and center-based; training: fine motor tasks	8	1/wk	NR	2 h/d, 6 d/wk	NDT: wt bearing, facilitation arm movement; context: home	8	1/wk	1–2 h	NR
Lin et al[31]	Restraint: elastic bandage; context: home; training: repetitive task practice	4	2/wk	4 h	4 h/d	Therapy, functional activities, NDT, motor learning; context, home	4	2/wk	4 h	4 h/d
Sakzewski et al[32,33]	Restraint: mitt; context: community groups of 8 to13; training: repetitive task practice, circus themed	2	5/wk	6 h	Nil	BIM; context, community groups of 8–13; training, repetitive bimanual activities	2	5/wk	6 h	Nil
Wallen et al[37]	Restraint: mitt; context: home, school, preschool; training: goal-directed, ADLs, repetitive movements in play	8	1/wk	1 h	2 h/d, 7 d/wk	OT: goal-directed, stretch, splint, motor training, environmental modification	8	1/wk	1 h	0.3 h/d
Gordon et al[58] and de Brito Brandão et al[36]	Restraint: sling; context: day camps, groups of 2 to 5; training: unimanual functional, and play	3	5/wk	6 h	1 h/d for 6 mo	BIM: goal-directed, symmetrical and asymmetric	3	5/wk	6 h	1 h/d for 6 mo

TABLE 2 Continued

Study	Content of Intervention Program	Duration, wk	Frequency of Sessions	Intensity	Home Program	Content of Control Group	Duration, wk	Frequency of Sessions	Intensity	Home Program
Eliasson et al (a)[40]	Eco-CIMT first Restraint: glove; context: individual home- or community- based; training: based on AHA assessment, repetitive whole-task practice	8	7/wk		2 h with weekly supervision by therapist	Usual care: ADLs, fine motor training, functional activity-based	8	1/m OT 2/m PT	NR	NR
Eliasson et al (b)[40]	Eco-CIMT second	8	7/wk		2 h as above	Usual care: a/a	8	1/m OT 2/m PT	NR	NR
Facchin et al (c)[38] and Fedrizzi et al[39]	Restraint: glove; context: individual; training: holding, manipulation, ADLs	10	3/wk	3 h	3 h/d for 4 d	BIM	10	3/wk	3 h	3 h/d for 4 d
Facchin et al (c)[38] and Fedrizzi et al[39]	Restraint: glove; context: individual; training: a/a	10	3/wk	3 h	3 h/d for 4 d	Usual care	10	1-2/wk	1 h	NR
Facchin et al (c)[38] and Fedrizzi et al[39]	BIM; bimanual holding, manipulation, ADLs	10	3/wk	3 h	3 h/d for 4 d	Usual care	10	1-2/wk	1 h	NR
Xu et al (a)[41]	Restraint: splint; context: hospital in groups of 2 to 4; training: structured play and functional activities; FES: 50 Hz pulse rate, 30 pulse/s, 300 μs amplitude, 12 s on time, 12 s off time	2	5/wk	3 h (mCIMT); 0.3 h (FES)	1 h/d with restraint during CIMT 2 h/d for 6 mo after CIMT	CIMT as per treatment group, no FES	2	5/wk	3 h	1 h/d with restraint during CIMT, 2 h/d for 6 mo after CIMT
Xu et al (b)[41]	Restraint: splint; context: hospital in groups of 2 to 4; training, structured play and functional activities	2	5/wk	3 h		OT: NDT, task-specific training, strength, stretch	2	5/wk	3 h	Time not specified
Hsin et al[42] and Chen et al[43]	Restraint: elastic bandage and glove; context: home; training: shaping and repetitive task practice	4	2/wk	3.5–4 h	3.5–4 h/d for 3 d/wk	Traditional rehab: NDT, task training; context: home	4	2/wk	3.5-4 h	Time not specified
Rostami et al (a)[44]	Restraint: splint; context: home-based individual; training: reach, grasp, manipulate, fine motor, ADLs	3	3/wk	1.5 h	1 h/d	mCIMT Restraint: splint; context: clinic-based; training as per intervention group	3	3/wk	1.5 h	1 h/d

TABLE 2 Continued

Study	Content of Intervention Program	Duration, wk	Frequency of Sessions	Intensity	Home Program	Content of Control Group	Duration, wk	Frequency of Sessions	Intensity	Home Program
Rostami et al (b)[45]	mCIMT: details a/a	4	3/wk	1.5 h	5 h/d restraint	CIMT and VR: E-Link Evaluation and Exercise System: active, active resistive grip and pinch, ROM exercises	4	3/wk	1.5 h	NR
Rostami et al (c)[45]	mCIMT: details a/a	4	3/wk	1.5 h	5 h/d restraint	Control group: NDT, stretching, ROM	4	1/wk	1 h	NR
Choudhary et al[46]	Restraint: arm sling; context: groups of 4; training: repetitive task practice, shaping	4	2–3/wk	2 h	1 h/d (10 d) 2 h/d (30 d)	Regular therapy: stretch, strength, bilateral hand tasks provided by parents at home	4	5/wk		20
Hoare et al[47]	Botox injections: maximum dose, 15 U/kg; dilution, 100 U/mL; therapy, mCIMT; restraint, glove; context: individual, hospital- based, and home	8	2/wk	1 h	Glove and home practice 21 h/wk	Botox injections and bimanual OT: motor learning and cognitive-based; context: individual hospital-based	8	2/wk	1 h	Time not specified
Hybrid model: combined mCIMT and bimanual training										
de Brito Brandão et al[9]	Hybrid Restraint: resting splint and sling; context, individual; training, shaping of fine motor, ADLs	2 mCIMT 1 BIM	5/wk 3/wk	4 h 0.75 h	Restraint worn 10 h/d for 2 wk	Usual care, bimanual activities, sensory stimulation	3	1/wk	0.75 h	NR
Aarts et al[8]	mCIMT-BIT Restraint: sling; context: rehab center in groups of 6; training: mCIMT 6 wk repetitive task practice, BIM 2 wk, goal-directed	6 mCIMT 2 BIM	3/wk	3 h	Expected duration NR	Usual care: stretch, wt bearing, bimanual therapy	8	2/wk	1.5 h	1 h/d
Forced-use therapy										
Sung et al[48]	Forced-use therapy Restraint: short arm cast; therapy: stretch, reach, grasp, manipulate, functional training	6	2/wk	0.5 h	NR	OT as per intervention group	6	2/wk	0.5 h	NR
Eugster-Buesch et al[49]	Restraint: removable cast; regular therapy	2	7/wk 1/wk	6 h NR	ADLs 2 h/d	Control group	2	1/wk	NR	NR

TABLE 2 Continued

Study	Content of Intervention Program	Duration, wk	Frequency of Sessions	Intensity	Home Program	Content of Control Group	Duration, wk	Frequency of Sessions	Intensity	Home Program
Other UL interventions										
Gordon et al[50]	HABIT; context: groups of 4; training: bilateral fine motor, manipulative gross motor activities	2	5/wk	6 h	1 h/d 2 h/d post treatment of 1 mo	Maintained previous levels	2	NR	NR	NR
Novak et al (a)[51]	OT home program: goal-directed, parent education, handwriting, strength, play	8	0.6/wk		0.25 h/session (mean)	Control group	8	NR	NR	NR
Novak et al (b)[51]	OT home program: details as above	4	0.6/wk		0.25 h/session (mean)	Control group	8	NR	NR	NR
Elliott et al[52]	Second skin lycra splint, goal-directed training embedded in daily routine	12	5/wk	6 h (splint)	0.4 h (training)	Goal-directed training	12	5/wk		0.4 h
Law et al[53]	Child-focused Remediation of impairments using stretch, cast, strength, wt bearing, and facilitation of normal movement	26	0.7–0.9/wk	NR	NR	Context-focused: goal-directed, task and environment adaptation	26	0.7 to 0.9/wk	NR	NR
Gygax et al (a)[54]	Mirror therapy and bimanual activities first: bilateral thumb-fingers pinch and grasp and pronation supination; context: home	3	7/wk		0.25 h	Bimanual activities as per treatment group, no mirror; context: home	3	7/wk		0.25 h
Gygax et al (b)[54]	Mirror therapy and bimanual activities second	3	7/wk		0.25 h	a/a	3	7/wk		0.25 h
Duncan et al[55]	Acupuncture: massage, scalp and body acupuncture; therapy: OT, fine motor tasks, ADLs; hydro	3	5/wk	0.5 h OT 0.5 h PT 0.5 h hydro		Therapy: OT, fine motor, ADLs; hydro	3	5/wk	0.5 h OT 0.5 h PT 0.5 h hydro	
Buccino et al[56]	Action observation and usual care	3	5/wk	NR	NR	Sham video and usual care	3	5/wk	NR	NR
Rostami et al (d)[45]	VR: E-Link Evaluation and Exercise System: active, active resistive grip and pinch, ROM exercises	4	3/wk	1.5 h	NR	Control group: NDT, stretching, ROM	4	1/wk	1 h	NR

a/a, as above; ADLs, activities of daily living; BIM, bimanual; Eco, ecological; hydro, hydrotherapy; NR, not reported; PT, physiotherapy; rehab, rehabilitation; ROM, range of motion; VR, virtual reality; Zancolli IIB: no active wrist extension with fingers flexed.

OT alone (n = 53), with an SMD of 0.30 (95% CI: −0.09 to 0.70; P = .14). Goal Attainment Scale scores were pooled from 4 studies that compared BoNT-A and OT (n = 73) with OT alone (n = 71) and received an SMD of 0.92 (95% CI: 0.57 to 1.27; $P < .0001$). At 6 months postintervention, a moderate effect was sustained (SMD: 0.56; 95% CI: −0.01 to 1.13; P = .06). A small treatment effect favoring bimanual training (n = 39) over an equal dose of mCIMT (n=40) was found with pooled data from 2 studies on the COPM performance and satisfaction scales (SMD [95% CI]: −0.13 [−0.58 to 0.31; P = .55] and −0.24 [−0.68 to 0.20; P = .29], respectively). There was a negligible effect of mCIMT compared with a comparison group (unequal dose) for data pooled from 2 studies for COPM performance (SMD: 0.05; 95% CI: −0.38 to 0.48; P = .83).

Self-Care Outcomes

Results of studies reporting self-care outcomes are summarized in Table 7. Data were pooled from 3 studies of BoNT-A and OT (n = 62) compared with OT alone (n = 60), with an SMD of −0.03 (95% CI: −1.09 to 0.22; P = .94).

Adverse Events and Clinical Feasibility and Acceptability

Short-acting and reversible adverse events reported after BoNT-A injections included nausea and vomiting[18,19,47] and transient weakness.[14,19,20,47] Minor skin irritations were reported after casting for cCIMT.[6] Poor tolerance with wearing a mitt/constraint in mCIMT was reported in 5 studies (8%–20% of cohort).[7,29,31,37,40] Difficulties achieving the proposed dose of home practice/constraint wear were reported in studies of mCIMT,[7,30,37,40,47] ranging from achievement of 50%[7,30] to 80%[35] of the anticipated dose.

DISCUSSION

This updated systematic review of nonsurgical UL interventions in children with unilateral CP highlighted an almost fourfold increase in publications since the previous review published in 2009. Forty-two RCTs reporting 14 types of UL rehabilitation with a total of 1454 participants met a priori inclusion criteria.

The greatest increase in publications has been for contemporary, motor-learning–based approaches (cCIMT, mCIMT, hybrid models, HABIT). Individually, these studies have predominantly reported improved UL outcomes compared with usual care delivered at a substantially lower dosage. Results of meta-analyses revealed modest to large effects of mCIMT on improving efficiency and quality of movement of the impaired UL compared with usual care. Two studies, however, found minimal differences between groups. One compared an average of 114 hours of mCIMT to 47 hours of bimanual OT[47]; the other compared 72 hours of mCIMT to 44 hours of bimanual OT.[37] Together, these results suggest that 40 hours of therapy was adequate to yield meaningful clinical changes in UL and individualized outcomes. One study directly compared 126 with 63 hours of cCIMT in a small group of 3- to 6-year-old children and found that no benefit was conferred by the additional time.[27,28] The exact critical threshold dose of intervention required to achieve meaningful changes in UL function remains unknown.

Individually, studies comparing intensive unimanual therapy (CIMT, mCIMT) or hybrid therapy with standard care of a lesser dose have revealed modest to strong treatment effects across most UL outcomes.[6,8,26,45,46] In contrast, trials comparing intensive unimanual therapy (eg, mCIMT) with an equivalent dose of bimanual training have reported weak to modest treatment effects on most outcomes.[31,32,35,38] Results of meta-analyses confirmed minimal differences between these approaches, because both yielded similar UL improvements. Findings suggest that meaningful clinical outcomes may be related to dose of therapy rather than the specific treatment approach. Since our previous systematic review, a greater number of studies have reported valid and reliable outcomes, allowing pooling of data for meta-analyses. The Pediatric Motor Activity Log (PMAL) has been used in 8 studies of cCIMT or mCIMT, with strong ESs reported across individual trials. However, we chose to exclude the PMAL from meta-analysis. Significant concerns have been raised about the measure.[57] The original version[6] lacks sufficient evidence of reliability and validity. Subsequently, a revised version submitted to Rasch analysis was reported[58] in addition to a second alternative revision.[59] Both revisions were called PMAL-R, causing confusion over the version used in each study. A further validity study of the original PMAL found only fair criterion validity for the how well domain (how well the child uses their impaired UL) but suggested that the measure was markedly sensitive to change.[60] Because each version of the PMAL, however, has different items, rating scales, mode of administration, and overall limited psychometric data,[58] we chose to exclude these data from meta-analysis. Future studies using the PMAL to evaluate real-world use of the impaired UL should accurately cite the relevant version used.

Efforts to adapt CIMT to make the approach more clinically feasible have included reliance on home programs to augment direct therapy. Between 50% and 80% of the anticipated dose was achieved across studies relying on home practice. Qualitative data from 1 study indicated that ∼30% of caregivers found implementing home practice of mCIMT either difficult or very difficult.[37] In contrast, home practice of bimanual training (HABIT)

TABLE 3 Methodologic Quality Assessment of Included Studies of Nonsurgical UL Interventions for Children With Congenital Hemiplegia: PEDro Scale

Study	Score										Total
	1	2	3	4	5	6	7	8	9	10	
NDT											
Law et al (1991)[12]	1	0	1	0	0	1	1	1	1	1	7
Law et al (1997)[13]	1	0	1	0	0	1	1	1	1	1	7
BoNT-A											
Fehlings et al (2000)[14]	1	0	1	0	0	1	1	0	1	1	6
Speth et al (2005)[15]	1	1	1	0	0	1	1	0	1	1	7
Lowe et al (2006)[16]	1	1	0	0	0	1	1	1	1	1	7
Kawamura et al (2007)[17]	1	1	1	1	1	1	1	0	1	1	9
Wallen et al (2007)[18]	1	1	1	0	0	1	1	1	1	1	8
Russo et al (2007)[19]	1	1	1	0	1	1	1	1	1	1	9
Olesch et al (2009)[20]	1	1	0	0	0	1	1	1	1	1	7
Kanellopoulos et al (2009)[21]	1	0	0	0	0	0	1	0	1	0	3
Rameckers et al (2009)[24]	1	0	1	0	0	1	1	1	1	1	7
Pieber et al (2011)[22]	1	0	0	0	0	1	1	0	0	0	3
Elvrum et al (2012)[23]	1	0	0	0	0	0	1	0	1	1	4
cCIMT											
Taub et al (2004)[6]	1	0	1	0	0	0	1	0	1	1	5
DeLuca et al (2006)[25]	1	0	0	0	0	1	1	0	1	0	4
Taub et al (2011)[26]	1	0	1	0	0	0	1	0	1	1	5
Case-Smith et al (2012)[27]	1	1	0	0	0	1	1	0	1	1	6
DeLuca et al (2012)[28]	1	1	0	0	0	1	1	1	1	0	6
mCIMT											
Charles et al (2006)[7]	1	0	1	0	0	1	0	0	1	1	5
Smania et al (2009)[29]	1	0	0	0	0	1	1	0	1	1	5
Al-Oraibi et al (2011)[30]	1	0	0	0	0	1	0	0	1	1	4
Lin et al (2011)[31]	1	0	1	0	0	1	1	0	1	1	6
Sakzewski et al (2011a)[32]	1	1	1	0	0	1	1	1	1	1	8
Sakzewski et al (2011b)[33]	1	1	1	0	0	0	1	1	1	1	7
Sakzewski et al (2011c)[34]	1	1	1	0	0	1	1	1	1	1	8
Wallen et al (2011)[37]	1	1	1	0	0	1	1	1	1	1	8
Gordon et al (2011)[35]	1	1	1	0	0	1	1	1	1	1	8
Eliasson et al (2011)[40]	1	0	1	0	0	1	1	0	1	1	6
Facchin et al (2011)[38]	1	0	1	0	0	1	1	0	1	0	5
Fedrizzi et al (2012)[39]	1	0	1	0	0	1	1	0	1	1	6
Xu et al (2012)[41]	1	0	1	0	0	1	1	0	1	1	6
Hsin et al (2012)[42]	1	1	1	0	0	1	1	0	1	1	7
Chen et al (2012)[43]	1	0	1	0	0	1	1	0	1	1	6
de Brito Brandão et al (2012)[36]	1	1	1	0	0	0	1	0	1	1	6
Rostami et al (2012a)[44]	1	0	1	0	0	1	0	0	1	1	5
Rostami et al (2012b)[45]	1	1	1	0	0	1	1	1	1	1	8
Choudhary et al (2012)[46]	1	1	1	0	0	1	1	1	1	1	8
Hoare et al (2012)[47]	1	1	1	0	0	1	1	1	1	1	8
Hybrid model: combined mCIMT and bimanual training											
de Brito Brandão et al (2010)[9]	1	1	1	1	0	0	1	1	1	1	8
Aarts et al (2010)[8]	1	0	1	0	0	1	1	0	1	1	6
Forced-use therapy											
Sung et al (2005)[48]	1	0	1	0	0	0	0	0	1	1	4
Eugster-Buesch et al (2012)[49]	1	1	1	0	0	1	1	0	1	1	7
Other UL interventions											
Gordon et al (2007)[50]	1	0	0	0	0	1	1	0	1	1	5
Novak et al (2010)[51]	1	1	1	0	0	1	1	1	1	1	8
Elliott et al (2011)[52]	1	0	1	0	0	0	1	1	1	1	6
Law et al (2011)[53]	1	1	1	0	0	1	1	1	1	1	8
Gygax et al (2011)[54]	1	0	1	0	0	0	1	0	1	1	5
Duncan et al (2012)[55]	1	1	1	0	0	1	0	1	1	1	7
Buccino et al (2012)[56]	1	0	0	1	0	1	1	0	1	0	5

Scale of item score 0 = absent, 1 = present. The PEDro scale criteria are as follows: (1) random allocation, (2) concealed allocation, (3) similarity at baseline on key measures, (4) subject blinding, (5) therapist blinding, (6) assessor blinding, (7) >85% follow-up of at least 1 key outcome, (8) intention-to-treat analysis, (9) between-group statistical comparison for at least 1 key outcome, (10) point estimates and measures of variability provided for at least 1 key outcome.

achieved 85% of the dose, which may suggest that bimanual home practice is easier to implement than mCIMT. Reported difficulties surrounding tolerance with wearing constraint may contribute to adherence to mCIMT home programs. Results of 1 high-quality RCT of OT home programs provided clinicians with guidelines on developing home programs that have been adopted in a number of mCIMT studies.[37,47] Five steps in developing home programs have been proposed, including collaborative partnerships between therapist and caregivers, mutually agreed-upon goals, activity selection to achieve goals, supporting caregivers, and evaluating outcomes.[51] Results, again, highlight the importance of activity-based, goal-directed therapy as integral in UL rehabilitation for children with unilateral CP.

Variation across studies of mCIMT, cCIMT, HABIT, and hybrid interventions was present in the following models of therapy: (1) short-duration, highly intensive group- or individual-based treatment versus a distributed longer-duration, less-intensive intervention; and (2) clinic-based versus home/context-based intervention. One study directly compared home- with clinic-based mCIMT in a small group of children with unilateral CP. Findings suggested some additional benefit of home- over clinic-based therapy in continued improvement in UL function to 3 months postintervention.[44] Embedding intervention in natural environments (eg, home, preschool/school) has been suggested to lead to meaningful, generalizable improvements in function.[51] Home-based mCIMT and bimanual OT were investigated, with promising results.[31,37,40,47] It remains unclear whether there are differences in efficacy of intensive versus distributed models of therapy, and between interventions primarily providing direct hands-on therapy by therapists and indirect therapy relying on caregivers

TABLE 4 Summary of Results of Studies of Nonsurgical UL Interventions Reporting on UL Outcomes

Study	Outcome	Timing, wk	*n*	Treatment, Mean (±SD)	*n*	Control, Mean (±SD)	SMD (95% CI)	*P*
NDT								
Law et al[12] (a)	PFMS	26	19	35.4 (13.9)	18	28.1 (18.4)	0.43 (−0.21 to 1.09)	
	QUEST			66.8 (23)	18	47.9 (26.8)	0.74 (0.08 to 1,41)	.03
Law et al[12] (b)	PFMS	26	17	33.7 (20.1)	18	30.8 (21.3)	0.13 (−0.53 to 0.80)	
	QUEST			50.9 (25.7)		47.2 (28.9)	0.13 (−0.53 to 0.80)	
Law et al[13] (a)	PFMS	16	26	21.8 (8.5)	24	20.9 (9.0)	0.10 (−0.45 to 0.66)	
	QUEST			53.3 (22.9)		47.3 (27.7)	0.23 (−0.32 to 0.79)	
Law et al[13] (b)	PFMS	40	26	24.7 (13.4)	24	24.9 (12.3)	−0.02 (−0.57 to 0.54)	
	QUEST			53.3 (25.1)		49.0 (24.4)	0.17 (−0.38 to 0.73)	
BoNT-A								
Fehlings et al[14]	QUEST	4	14	32.54 (17.8)	15	27.6 (19.0)	0.26 (−0.47 to 0.99)	
		12		28.5 (20.2)		30.4 (19.6)	−0.10 (−0.82 to 0.64)	
		26		30.7 (18.8)		34.4 (24.4)	−0.17 (−0.89 to 0.57)	
Speth et al[15a]	MelbA	2	10	67.7 (58, 79)	10	60.3 (44, 79)	Not estimable	
		6		68.5 (56, 77)		65.6 (48, 81)	Not estimable	
		12		72.1 (49, 82)		64.4 (48, 76)	Not estimable	
		24		68.9 (56, 83)		66.6 (49, 78)	Not estimable	
		36		68.5 (49, 82)		62.7 (48, 85)	Not estimable	
Lowe et al[16]	QUEST	4	21	43.9 (15.1)	21	36 (12.4)	0.55 (−0.07 to 1.17)	
		12		46.2 (16)		37.1 (11.9)	0.65 (0.01 to 1.25)	.04
		26		40.7 (14.7)		39.6(12.8)	0.08 (−0.53 to 0.68)	
Kawamura et al[17]	QUEST-T	4	18	49.8 (16.0)	21	47.8 (18.8)	0.11 (−0.52 to 0.74)	
		12		51.3 (14.0)		48.3 (19.2)	0.18 (−0.55 to 0.91)	
Wallen et al[18] (a)[b]	MelbA	12	13	63.69 (20.9)	9	61.4 (21.2)	0.18 (−0.67 to 1.03)	
		26	7	64.26 (24.2)	6	58.7 (23.8)	0.23 (−0.63 to 1.07)	
	QUEST	12		67.5 (17.4)		30.6 (35)	2.12 (0.76 to 3.48)	.00
		26		62.1 (23.6)		30.6 (30.4)	1.17 (−0.8 to 2.26)	
Wallen et al[18] (b)[c]	MelbA	12	11	57.4 (24.8)	11	63.5 (29.0)	−0.22 (−1.06 to 0.62)	
		26		58.0 (23.4)		64.8 (30.0)	−0.25 (−1.08 to 0.6)	
	QUEST	12	9	34.5 (38)	6	39.4 (20.6)	−0.14 (−1.18 to 0.89)	
		26		28.3 (32.8)	7	36.7 (31.7)	−0.26 (−1.24 to 0.75)	
Olesch et al[20]	QUEST-DM	16	11	80.1 (13.3)	11	73.8 (13.9)	0.46 (−0.40 to 1.29)	
		32		76.6 (9.5)		74 (13.2)	0.23 (−0.60 to 1.06)	
		48		79.9 (10.9)		74.9 (11.8)	0.44 (−0.42 to 1.27)	
	QUEST-G	16		68.4 (13.1)		65.3 (11.9)	0.25 (−0.60 to 1.08)	
		32		71.4 (14.8)		68.4 (12.7)	0.22 (−0.63 to 1.05)	
		48		73.4 (11)		60.9 (16.3)	0.91 (0.00 to 1.75)	
	QUEST-T	16		76.3 (13.2)		70.8 (12.8)	0.42 (−0.44 to 1.25)	
		32		76.9 (10.4)		69.3 (13.4)	0.63 (−0.25 to 1.46)	
		48		79.6 (8.0)		72.9 (11.5)	0.68 (−0.21 to 1.51)	
	PFMS	16		519.6 (25.3)		513.1 (33.8)	0.22 (−0.63 to 1.05)	
		32		524.8 (26.7)		528.7 (36)	−0.12 (−0.95 to 0.72)	
		48		542.6 (36.2)		537.6 (37.2)	0.14 (−0.71 to 0.97)	.05
Kanellopoulos[21] et al	QUEST	8	10	76.6 (9.1)	10	78.9 (14.4)	−0.19 (−1.06 to 0.7)	
		26		71.5 (10.7)		79.4 (14.9)	−0.61 (−1.48 to 0.31)	
Rameckers et al[24]	MelbA	26	10	68.4 (9.2)	10	65.6 (10.8)	0.28 (−0.61 to 1.15)	
		32		68.7 (10.2)		64.4 (13.6)	0.36 (−0.54 to 1.23)	
Elvrum et al[23]	MelbA	8	5	84.2 (8.5)	5	80.0 (8.4)	0.50 (−0.81 to 1.70)	
		20		85.3 (10.0)		79.8 (9.9)	0.55 (−0.84 to 1.83)	
	AHA	8		64.6 (12.5)		62.6 (10.4)	0.17 (−1.08 to 1.40)	
		20		66.0 (13.6)		61.8 (11.6)	0.34 (−1.02 to 1.62)	
cCIMT								
Taub et al[6]	PMAL-amt	0.4	9	2.8 (1.1)	9	1.2 (0.8)	1.54 (0.49 to 2.60)	.00
		3		2.6 (1.3)		1.2 (0.7)	1.36 (0.28 to 2.31)	.01
	PMAL-qual	0.4		2.7 (1.0)		1.8 (1.1)	0.73 (−0.23 to 1.68)	
		3		2.6 (1.3)		1.8 (1.0)	0.70 (−0.28 to 1.62)	
	EBS	0.4		21.5 (4.5)		15 (5.7)	1.22 (0.22 to 2.23)	.02
Taub et al[26]	PMAL-qual	4	10	3.5 (0.6)	10	1.4 (0.5)	3.8 (2.21 to 5.09)	.00
	INMAP	4		35.9 (6.2)		27.8 (6.6)	1.27 (0.26 to 2.17)	.01
	PAFT-use	4		45 (32.6)		15 (12.9)	1.21 (0.21 to 2.11)	.01
	PAFT-FA	4		2.6 (0.4)		2.1 (0.6)	0.98 (0.02 to 1.86)	.04

TABLE 4 Continued

Study	Outcome	Timing, wk	*n*	Treatment, Mean (±SD)	*n*	Control, Mean (±SD)	SMD (95% CI)	*P*
Case-Smith et al[27] and DeLuca et al[28]	QUEST-G	1	9	4.5 (2.6)	9	5 (2.6)	−0.19 (−1.11 to 0.74)	
		4		5.3 (3.1)		5.7 (3.0)	−0.13 (−1.05 to 0.80)	
		26		6.1 (2.9)		5.9 (3.6)	0.06 (−0.87 to 0.98)	
	QUEST-DM	1		22.1 (6)		21.9 (9.1)	0.03 (−0.90 to 0.95)	
		4		22.3 (6.3)		23.2 (8.5)	−0.12 (−1.04 to 0.81)	
		26		19.9 (5.5)		22.6 (7.2)	−0.42 (−1.33 to 0.53)	
	PMAL-amt	1		3.1 (1.3)		3.6 (1.0)	−0.43 (−1.34 to 0.52)	
		4		3.2 (1.2)		3.4 (1.0)	−0.28 (−1.20 to 0.66)	
		26		3.1 (1.2)		3.5 (1.3)	−0.32 (−1.23 to 0.62)	
	PMAL-qual	1		3.4 (1.4)		3.4 (0.8)	0.0 (−0.92 to 0.92)	
		4		3.0 (1.1)		3.7 (1.1)	−0.64 (−1.55 to 0.34)	
		26		3.1 (1.2)		3.6 (1.4)	−0.38 (−1.30 to 0.57)	
	AHA	1		0.8 (3.3)		3.0 (3.9)	−0.61 (−1.52 to 0.36)	
		4		1.1 (3.8)		2.6 (3.7)	−0.40 (−1.31 to 0.55)	
		26		1.4 (3.2)		3.1 (4.1)	−0.47 (−1.38 to 0.49)	
mCIMT								
Charles et al[7]	Jebsen	1	11	278.5 (240.6)	11	301 (182.2)	0.10 (−0.73 to 0.94)	
		4		268.6 (238)		260.3 (153)	−0.04 (−0.88 to 0.80)	
		26		272.5 (236.6)		297 (200)	0.11 (−0.73 to 0.94)	
	BOTMP	1		7.2 (2.9)		5.2 (4.2)	0.53 (−0.32 to 1.38)	
		4		7.6 (4.4)		5.5 (4.1)	0.49 (−0.37 to 1.32)	
		26		6.9 (3.7)		6.3 (5.1)	0.13 (−0.71 to 0.97)	
Al Oraibi et al[30]	AHA	Post (NR)	7	48 (11.7)	7	56.6 (18.7)	−0.55 (−1.58 to 0.55)	
Lin et al[31]	BOTMP-8	1	10	11.6 (9.4)	11	7.23 (8.4)	0.49 (−0.4 to 1.34)	
		26		10 (8.9)		7.1 (9.3)	0.32 (−0.56 to 1.16)	
	PDMS-G	1		45.9 (7.8)		44.3 (6.2)	0.23 (−0.64 to 1.08)	
		26		46.4 (7.4)		44 (6.2)	0.35 (−0.52 to 1.20)	
	PDMS-V	1		118.9 (26.6)		113.1 (23.4)	0.23 (−0.64 to 1.08)	
		26		122.9 (25.2)		113.7 (23.2)	0.38 (−0.5 to 1.23)	
	PMAL-amt	1		2.75 (1.1)		2.1 (1.0)	0.57 (−0.32 to 1.42)	
		26		3.1 (1.0)		2.3 (1.2)	0.73 (−0.19 to 1.58)	
	PMAL-qual	1		2.8 (1.0)		2.3 (0.9)	0.63 (−0.27 to 1.48)	
		26		3.2 (0.9)		2.2 (1.0)	1.01 (0.06 to 1.87)	.03
	CFUS-amt	1		2.7 (1.1)		2.6 (1.2)	0.09 (−0.77 to 0.94)	
		26		3.2 (1.0)		2.5 (1.1)	0.70 (−0.18 to 1.53)	
	CFUS-qual	1		2.7 (1.1)		2.4 (1.0)	0.35 (−0.53 to 1.20)	
		26		3.0 (0.9)		2.5 (0.9)	0.51 (−0.38 to 1.35)	
Sakzewski et al[32]	MelbA	3	31	69 (12.4)	31	71.5 (9.7)	−0.17 (−0.67 to 0.33)	
		26		71.1 (11.7)		71 (11.0)	0.01 (−0.51 to 0.52)	
		52		68.9 (12.4)		74.6 (11.8)	−0.47 (−0.06 to 0.99)	
	Jebsen	3	32	382.5 (203.8)		413.2 (179.8)	−0.16 (−0.65 to 0.34)	
		26		412.1 (190.0)		432.6 (177.3)	−0.11 (−0.63 to 0.41)	
		52		434.7 (196.9)		438 (180.3)	0.02 (−0.50 to 0.54)	
	AHA	3	31	64.8 (13.1)		64.9 (11.5)	−0.01 (−0.51 to, 0.49)	
		26		63.0 (13.9)		65.3 (11.5)	−0.18 (−0.69 to 0.34)	
		52		64.1 (11.7)		65.7 (12.6)	−0.13 (−0.65 to 0.39)	
Wallen et al[37]	PMALR-amt	10	25	57.5 (20)	25	51.5 (17.3)	0.32 (−0.24 to 0.87)	
		26		61.5 (18.5)		53.6 (16.1)	0.46 (−0.11 to 1.01)	
	PMALR-qual	10		59.6 (23.6)		51.3 (19.7)	0.38 (−0.18 to 0.94)	
		26		62.1 (22.5)		53.6 (16.1)	0.44 (−0.13 to 0.99)	
	AHA	10		62.9 (29.3)		52 (28.9)	0.37 (−0.19 to 0.93)	
		26		67.9 (26.3)		54.5 (26.9)	0.10 (−0.45 to 0.65)	

TABLE 4 Continued

Study	Outcome	Timing, wk	*n*	Treatment, Mean (±SD)	*n*	Control, Mean (±SD)	SMD (95% CI)	*P*
Gordon et al[58]	Jebsen	0.3	21	486.9 (184.9)	21	470.4 (184.9)	0.09 (−0.52 to 0.69)	
		4		512.9 (142.6)		483.1 (142.6)	0.21 (−0.40 to 0.81)	
		26		499 (165.5)		497.3 (165.5)	0.01 (−0.59 to 0.61)	
	QUEST-DM	0.3		90.3 (5.4)		91.2 (5.1)	−0.17 (−0.77 to 0.44)	
		4		91.3 (5.1)		90.8 (5.4)	0.10 (−0.51 to 0.70)	
		26		89.1 (6.3)		90.9 (6.3)	−0.29 (−0.89 to 0.33)	
	QUEST-G	0.3		80.6 (11.2)		79.4 (11.2)	0.11 (−0.50 to 0.71)	
		4		81.2 (10.5)		79.9 (10.5)	0.12 (−0.48 to 0.73)	
		26		78.8 (14.5)		76.2 (14.3)	0.18 (−0.43 to 0.78)	
	AHA	0.3		0.8 (1.8)		0.94 (1.8)	−0.08 (−0.68 to 0.53)	
		4		0.9 (1.8)		0.98 (1.8)	−0.04 (−0.65 to 0.53)	
		26		1.05 (1.6)		0.99 (1.6)	−0.04 (−0.57 to 0.64	
Eliasson et al[40]	AHA	1	12	59 (9)	13	46 (21)	0.79 (−0.05 to 1.58)	
		32		56 (19)		63 (7)	−0.48 (−1.26 to 0.33)	
Facchin et al[38d] and Fedrizzi et al[39] (a)	QUEST-T	1	39	76.3 (14.9)	33	70.0 (20.3)	0.36 (−0.11 to 0.82)	
		12		73.8 (16.7)		71.4 (19.1)	0.13 (−0.33 to 0.60)	
		26		76.1 (15.2)		74.6 (18.3)	0.09 (−0.37 to 0.55)	
	QUEST-G	1		72.1 (18.8)		66.9 (22.1)	0.26 (−0.21 to 0.72)	
		12		70.8 (18.7)		67.6 (20.7)	0.16 (−0.30 to 0.63)	
		26		69.2 (21.3)		68.9 (24.0)	0.01 (−0.45 to 0.48)	
	Besta-T	1		2.6 (0.8)		2.7 (0.9)	−0.15 (−0.61 to 0.32)	
		12		2.7 (0.8)		2.8 (0.9)	−0.16 (−0.62 to 0.31)	
		26		2.7 (0.8)		2.9 (0.9)	−0.23 (−0.69 to 0.24)	
	Besta-G	1		3.2 (0.7)		2.9 (0.9)	0.36 (−0.11 to 0.82)	
		12		3.1 (0.7)		3.0 (0.9)	0.22 (−0.24 to 0.69)	
		26		3.1 (0.7)		3.0 (0.9)	0.14 (−0.33 to 0.60)	
	Besta-Bim	1		2.8 (0.8)		2.9 (0.8)	−0.22 (−0.69 to 0.24)	
		12		2.7 (0.9)		2.9 (0.9)	−0.22 (−0.68 to 0.25)	
		26		2.8 (0.8)		3.1 (0.9)	−0.33 (−0.79 to 0.14)	
Facchin et al[38e] and Fedrizzi et al[39] (b)	QUEST-T	1	39	76.3 (14.9)	33	72.6 (17.7)	0.23 (−0.79 to 0.14)	
		12		73.8 (16.7)		68 (15.9)	0.35 (−0.12 to 0.82)	
		26		76.1 (15.2)		71.3 (15.7)	0.31 (−0.16 to 0.77)	
	QUEST-G	1		72.1 (18.8)		66.1 (20.8)	0.30 (−0.17 to 0.77)	
		12		70.8 (18.7)		62.4 (16.5)	0.47 (0.00 to 0.94)	.05
		26		69.2 (21.3)		66.5 (19.9)	0.14 (−0.33 to 0.60)	
	Besta-T	1		2.6 (0.8)		2.71 (0.8)	−0.12 (−0.58 to 0.35)	
		12		2.7 (0.8)		2.68 (0.7)	−0.03 (−0.49 to 0.44)	
		26		2.7 (0.8)		2.7 (0.8)	−0.05 (−0.52 to 0.41)	
	Besta-G	1		3.2 (0.7)		3.0 (0.8)	0.20 (−0.27 to 0.66)	
		12		3.1 (0.7)		3.1 (0.7)	0.11 (−0.35 to 0.57)	
		26		3.1 (0.7)		3.1 (0.7)	0.10 (−0.37 to 0.56)	
	Besta-Bim	1		2.8 (0.8)		3.0 (0.7)	−0.35 (−0.81 to 0.12)	
		12		2.7 (0.9)		3.0 (0.7)	−0.29 (−0.76 to 0.18)	
		26		2.8 (0.8)		2.9 (0.7)	−0.21 (−0.67 to 0.26)	
Facchin et al[38f] and Fedrizzi et al[39] (c)	QUEST-T	1	33	70.0 (20.3)	33	72.6 (17.7)	−0.14 (−0.62 to 0.35)	
		12		71.4 (19.1)		68 (15.9)	0.19 (−0.29 to 0.67)	
		26		74.6 (18.3)		71.3 (15.7)	0.19 (−0.29 to 0.67)	
	QUEST-G	1		66.9 (22.1)		66.1 (20.8)	0.04 (−0.45 to 0.52)	
		12		67.6 (20.7)		62.4 (16.5)	0.28 (−0.21 to 0.76)	
		26		68.9 (24.0)		66.5 (19.9)	0.11 (−0.38 to 0.59)	
	Besta-T	1		2.7 (0.9)		2.7 (0.8)	0.04 (−0.45 to 0.52)	
		12		2.8 (0.9)		2.7 (0.7)	0.15 (−0.34 to 0.63)	
		26		2.9 (0.9)		2.7 (0.8)	0.20 (−0.28 to 0.68)	
	Besta-G	1		2.9 (0.9)		3.0 (0.8)	−0.16 (−0.64 to 0.33)	
		12		3.0 (0.9)		3.1 (0.7)	−0.12 (−0.60 to 0.36)	
		26		3.0 (0.9)		3.1 (0.7)	−0.05 (−0.53 to 0.43)	
	Besta-Bim	1		2.9 (0.9)		3.0 (0.7)	−0.11 (−0.59 to 0.38)	
		12		2.9 (0.9)		3.0 (0.7)	−0.05 (−0.53 to 0.43)	
		26		3.0 (0.9)		2.9 (0.7)	0.15 (−0.33 to 0.64)	

TABLE 4 Continued

Study	Outcome	Timing, wk	*n*	Treatment, Mean (±SD)	*n*	Control, Mean (±SD)	SMD (95% CI)	*P*
Rostami et al[44] (a)	PMAL-amt	0.1	7	2.1 (0.5)	7	2.2 (0.3)	0.0 (−1.05 to 1.05)	
		12		3.0 (0.4)		2.2 (0.3)	2.26 (0.8 to 3.41)	.00
	PMAL-qual	0.1		2.3 (0.3)		2.2 (0.3)	0.3 (−0.74 to 1.36)	
		12		3.2 (0.4)		2.1 (0.2)	3.48 (1.64 to 4.83)	.00
	BOTMP-5	0.1		0.6 (0.2)		0.7 (0.2)	−0.5 (−1.53 to 0.6)	
		12		1.1 (0.2)		0.7 (0.2)	2.0 (0.61 to 3.11)	.00
	BOTMP-8	0.1		1.6 (0.2)		1.5 (0.2)	0.5 (−0.6 to 1.53)	
		12		2.3 (0.2)		1.6 (0.2)	3.5 (1.66 to 4.85)	.00
Rostami et al[45] (b)[g]	PMAL-amt	0.1	8	2.5 (0.51)	8	3.3 (0.32)	−1.88 (−2.93 to −0.62)	.00
		12		2.5 (0.29)		3.4 (0.46)	−2.31 (−3.43 to −0.95)	.00
	PMAL-qual	0.1		2.2 (0.19)		3.5 (0.28)	−5.18 (−6.86 to −2.94)	.00
		12		2.4 (0.14)		3.3 (0.19)	−5.69 (−7.49 to −3.27)	.00
	BOTMP-8	0.1		1.4 (0.37)		0.3 (0.08)	−1.54 (−2.56 to −0.35)	.01
		12		1.3 (0.12)		0.4 (0.07)	−2.73 (−3.91 to −1.25)	.01
Rostami et al[45] (c)[h]	PMAL-amt	0.1	8	2.54 (0.51)	8	0.8 (0.21)	4.49 (2.48 to 6.01)	.00
		12		2.5 (0.29)		0.8 (0.16)	7.0 (4.13 to 9.11)	.00
	PMAL-qual	0.1		2.2 (0.19)		0.7 (0.37)	5.27 (3.0 to 6.97)	.00
		12		2.4 (0.14)		0.7 (0.24)	8.4 (5.02 to 10.86)	.00
	BOTMP-8	0.1		1.4 (0.37)		0.3 (0.08)	4.0 (2.14 to 5.41)	.00
		12		1.3 (0.12		0.4 (0.07)	9.67 (5.83 to 12.46)	.00
Rostami et al[45] (d)[i]	PMAL-amt	0.1	8	2.4 (0.45)	8	0.8 (0.21)	4.5 (2.48 to 6.02)	.00
		12		2.3 (0.37)		0.8 (0.16)	5.02 (2.83 to 6.66)	.00
	PMAL-qual	0.1		2.3 (0.24)		0.7 (0.37)	5.13 (2.9 to 6.8)	.00
		12		2.2 (0.17)		0.7 (0.24)	7.36 (4.35 to 9.56)	.00
	BOTMP-8	0.1		1.2 (0.23)		0.3 (0.08)	5.46 (3.12 to 7.20)	.00
		12		1.3 (0.14)		0.4 (0.07)	8.22 (4.91 to 10.64)	.00
Xu et al[41] (a)[j] (change scores)	9-hole peg	2	23	8.1 (9.2)	22	6.1 (6.1)	0.26 (−0.34 to 0.84)	
		12		14.4 (16.2)		13 (12.5)	0.1 (−0.49 to 0.68)	
		26		22.3 (18.5)		30.7 (53.6)	−0.21 (−0.79 to 0.38)	
	PFMS-G	2		0.5 (0.7)		0.5 (0.9)	0 (−0.58 to 0.58)	
		12		1.7 (0.8)		1.3 (1.0)	0.44 (−0.16 to 1.03)	
		26		2.2 (1.1)		1.8 (1.0)	0.38 (−0.22 to 0.96)	
	PFMS-V	2		1.3 (1.5)		0.6 (1.1)	0.53 (−0.07 to 1.12)	
		12		3.7 (2.2)		2.4 (1.8)	0.65 (0.03 to 1.23)	.04
		26		5.8 (2.8)		3.7 (2.5)	0.79 (0.17 to 1.38)	.01
Xu et al[41] (b)[k] (change scores)	9-hole peg	2	23	6.1 (6.1)	23	2.7 (5.5)	0.59 (−0.02 to 1.17)	
		12		13 (12.5)		9.0 (9.6)	0.36 (−0.24 to 0.94)	
		26		30.7 (53.6)		14.0 (13.5)	0.43 (−0.17 to 1.02)	
	PFMS-G	2		0.5 (0.9)		0.4 (0.8)	0.12 (−0.47 to 0.7)	
		12		1.3 (1.0)		1.3 (0.8)	0 (−0.58 to 0.58)	
		26		1.8 (1.0)		1.8 (1.1)	0 (−0.58 to 0.58)	
	PFMS-V	2		0.6 (1.1)		0.3 (2.4)	0.16 (−0.43 to 0.74)	
		12		2.4 (1.8)		2.0 (2.5)	0.18 (−0.41 to 0.77)	
		26		3.7 (2.5)		2.8 (2.6)	0.35 (−0.24 to 0.94)	
Hsin et al[42] and Chen et al[43]	BOTMP-8	1	11	10.6 (1.6)	11	8.9 (1.1)	1.24 (0.28 to 2.10)	.01
		12	24	12.6 (1.6)	23	10.2 (1.5)	1.55 (0.54 to 2.43)	.00
	RPMAL-amt	1	11	2.5 (0.3)	11	2.3 (0.3)	0.67 (0.07 to 1.24)	.03
		12	24	2.9 (0.3)	23	2.8 (0.4)	0.28 (−0.57 to 1.11)	
	RPMAL-qual	1	11	2.4 (0.3)	11	2.2 (0.3)	0.67 (0.07 to 1.11)	.03
		12	24	3.0 (0.3)	24	2.7 (0.3)	1.00 (0.08 to 1.84)	.03
	PFMS-G	1		44.1 (2.8)		41.1 (3.1)	1.02 (0.39 to 1.61)	.00
	PFMS-VMI	1		135.4 (4.4)		128.0 (4.0)	1.76 (1.06 to 2.40)	.00
Choudhary et al[46]	QUEST total	4	16	87.2 (9.4)	15	82.5 (9.2)	0.51 (−0.22 to 1.21)	
		12		87.3 (10)		84.9 (8.3)	0.26 (−0.45 to 0.96)	
	QUEST-G	4		83.1 (10)		76.3 (9.3)	0.70 (−0.04 to 1.41)	
		12		83.3 (10.5)		78.5 (9.9)	0.47 (−0.26 to 1.17)	
	QUEST-DM	4		83.5 (10.8)		81.6 (12.2)	0.17 (−0.54 to 0.87)	
		12		83.4 (12.7)		82.9 (12.7)	0.04 (−0.67 to 0.74)	
	9-hole peg	4		105.4 (47.3)		151.5 (61.7)	−0.84 (−1.55 to −0.09)	.03
		12		95.1 (44.8)		137.4 (59.9)	−0.80 (−1.51 to −0.05)	.03

TABLE 4 Continued

Study	Outcome	Timing, wk	*n*	Treatment, Mean (±SD)	*n*	Control, Mean (±SD)	SMD (95% CI)	*P*
Hoare et al[47]	QUEST-DM	4	17	72.5 (12.0)	17	74.6 (14.7)	−0.16 (−0.83 to 0.52)	
		12		73.7 (16.5)		75 (13.9)	−0.08 (−0.76 to 0.59)	
		26		67.7 (16.4)		75.7 (12.7)	−0.54 (−1.22 to 0.15)	
	QUEST-G	4		57.2 (20.8)		57.7 (18.7)	−0.02 (−0.70 to 0.65)	
		12		55.7 (24.7)		59.4 (18.7)	−0.17 (−0.84 to 0.51)	
		26		61.2 (18.2)		56.7 (13.6)	0.28 (−0.4 to 0.95)	
	AHA	4		39.6 (16.5)		44.5 (17.3)	−0.29 (−0.96 to 0.39)	
		12		44.5 (17.1)		49.5 (12.4)	−0.33 (−1.0 to 0.35)	
		26		46.1 (15.3)		50.8 (11.5)	−0.35 (−1.02 to 0.34)	
Hybrid model: combined mCIMT and BIM								
de Brito Brandão et al[9]	Jebsen	1	8	115.2 (112.6)	7	180.4 (203.7)	−0.40 (−1.40 to 0.64)	
		4		90.5 (99.8)		146.1 (186.4)	−0.38 (−1.38 to 0.66)	
Aarts et al[36]	ABILHAND	9	28	28.4 (5.9)	24	23.7 (6.0)	0.79 (0.2 to 1.36)	.01
		17		28.9 (5.2)		24.4 (6.6)	0.77 (0.18 to 1.33)	.01
	MelbA	9		68.8 (11.6)		63.5 (16.7)	0.38 (−0.19 to 0.93)	
		17		69.1 (12)		65.1 (14.3)	0.31 (−0.26 to 0.86)	
	AHA	9		60.1 (15.3)		53.1 (22.2)	0.38 (−0.19 to 0.93)	
		17		59.7 (13.5)		52.3 (21.4)	0.43 (−0.15 to 0.98)	
Forced-use therapy								
Sung et al[48]	EDPT	1	18	7.6 (1.7)	13	7.1 (1.4)	0.37 (−0.36 to 1.08)	
	Box & Block			10.5 (5.7)		9.5 (7.1)	0.15 (−0.57 to 0.86)	
Eugster-Buesch et al[49] (change scores)	MelbA	Post (NR)	12	1.94 (4.86)	11	−0.05 (3.74)	0.45 (−0.39 to 1.27)	
		2		4.4 (4.68)		1.95 (3.97)	0.56 (−0.29 to 1.38)	
		12		1.96 (4.88)		1.84 (5.24)	0.02 (−0.80 to 0.84)	
Other UL interventions								
Gordon et al[50]	Jebsen	1	10	339.6 (182.9)	10	434.9 (230.1)	−0.46 (−1.33 to 0.45)	
		4		309.9 (155.7)		355.9 (151.3)	−0.30 (−1.21 to 0.64)	
	AHA	1		1.5 (1.8)		1.2 (2.1)	0.17 (−0.74 to 1.06)	
		4		0.95 (1.7)		1.8 (2.0)	−0.47 (−1.41 to 0.51)	
	BOTMP (6 BIM items)	1		5.6 (3.6)		8.4 (5.2)	−0.64 (−1.51 to 0.29)	
		4		7.1 (4.7)		8.7 (5.6)	−0.30 (−1.22 to 0.64)	
Novak et al[51] (a)	QUEST-T	4	12	70.2 (22.4)	12	26.0 (2.1)	1.12 (0.22 to 1.93)	.01
		8		71.3 (21.4)		26.0 (2.1)	1.16 (0.26 to 1.98)	.01
Novak et al[51] (b)	QUEST-T	4	11	55.4 (30.3)	12	26.0 (2.1)	0.35 (−0.49 to 1.16)	
		8		59.7 (26.8)		26.0 (2.1)	0.53 (−0.32 to 1.34)	
Gygax et al[54]	SHUEE-F	3	5	61.7 (30)	5	58.2 (27.5)	0.12 (−1.13 to 1.35)	
	SHUEE-P	3		71 (29.3)		68.4 (20.3)	0.10 (−1.15 to 1.33)	
	SHUEE-G	3		88.9 (23.6)		80 (28.2)	0.34 (−0.94 to 1.56)	

ABILHAND, ; -amt, amount of use; Besta-G; Besta Scale grasp; Besta-T, Besta Scale total; Besta-Bim; Besta Scale bilateral manipulation; BIM, bimanual training; BOTMP, Bruininks-Oseretsky Test of Motor Proficiency; CFUS, Caregiver Functional Use Survey; DM, dissociated movements domain; EBS, Emerging Behavior Scale; EDPT, Erhardt Developmental Prehension Test; G, grasp domain; Jebsen, Jebsen Taylor Hand Function Test; MelbA, Melbourne Assessment of Unilateral Upper Limb Function; NR, not reported; PAFT, pediatric arm function test; PFMS, Peabody Fine Motor Scales; PFMS-G; Peabody Fine Motor Scale grasp domain; PFMS-VMI; Peabody Fine Motor Scale visual motor integration domain; -qual, quality of use; PMAL-R revised Pediatric Motor Activity Log; PMAL, Pediatric Motor Activity Log; SHUEE-F, Shriner's Hospital for Children Upper Extremity Evaluation–spontaneous functional analysis; SHUEE-G, Shriner's Hospital for Children Upper Extremity Evaluation–grasp and release; SHUEE-P, Shriner's Hospital for Children Upper Extremity Evaluation–dynamic positional analysis.

[a] Data in Treatment and Control columns are presented as medians (interquartile range) for Speth et al[15].

[b] Wallen et al[18] (a) BoNT-A and OT versus control.

[c] Wallen et al[18] (b) BoNT-A and OT versus OT.

[d] Facchin et al[38] (a) mCIMT versus BIM.

[e] Facchin et al[38] (b) mCIMT versus control.

[f] Facchin et al[38] (c) BIM versus control.

[g] Rostami et al[45] (b) mCIMT versus mCIMT and virtual reality.

[h] Rostami et al[45] (c) mCIMT versus control.

[i] Rostami et al[45] (d) virtual reality versus control.

[j] Xu et al[41] (a) mCIMT and FES versus mCIMT.

[k] Xu et al[41] (b) mCIMT versus OT.

delivering intervention via home programs.

There was a modest supplementary effect of BoNT-A as an adjunct to OT to improve quality of movement of the impaired UL. Results were not replicated on the Melbourne Assessment; however, data were pooled from only 2 studies with small sample sizes. The sensitivity of the Melbourne Assessment to capture change has been questioned, because most UL studies failed to show the

TABLE 5 Summary of Meta-analyses

Outcomes	Number of Studies	Number of Participants	Statistical Method	Effect Size (95% CI)
Comparison 1: BoNT-A and OT versus OT alone				
QUEST, total score postintervention	4	108	SMD (IV, fixed, 95% CI)	0.35 (−0.03 to 0.73)
QUEST, total score 6 to 8 months postintervention	4	108	SMD (IV, fixed, 95% CI)	0.06 (−0.32 to 0.44)
Melbourne, 6 months postintervention	2	42	SMD (IV, fixed, 95% CI)	−0.00 (−0.61 to 0.61)
COPM-performance, postintervention	3	101	SMD (IV, fixed, 95% CI)	0.30 (−0.09 to 0.70)
COPM-performance, 6 months postintervention	2	79	SMD (IV, fixed, 95% CI)	0.12 (−0.32 to 0.57)
COPM-satisfaction, postintervention	3	101	SMD (IV, fixed, 95% CI)	0.29 (−0.10 to 0.68)
COPM-satisfaction, 6 months postintervention	2	79	SMD (IV, fixed, 95% CI)	0.08 (−0.36 to 0.53)
GAS, postintervention	4	144	SMD (IV, fixed, 95% CI)	0.92 (0.57 to 1.27)
GAS, 6 to 9 months postintervention	4	144	SMD (IV, random, 95% CI)	0.56 (−0.01 to 1.13)
PEDI Self-Care FSS, post intervention	3	112	SMD (IV, random, 95% CI)	−0.03 (−0.74 to 0,69)
PEDI Self-Care FSS, 6 months postintervention	3	112	SMD (IV, random, 95% CI)	0.06 (−0.3 to 0.42)
Comparison 2: CIMT or mCIMT versus control (unequal dose) or comparison (equal dose)				
QUEST-Grasp, postintervention				
a) Comparison equal dose	2	114	SMD (IV, fixed, 95% CI)	0.11 (−0.26 to 0.47)
b) Control (unequal dose)	3	137		0.30 (−0.04 to 0.64)
Total	5	241		0.21 (−0.04 to 0.46)
QUEST-Grasp, 6 months postintervention				
a) Comparison equal dose	2	114	SMD (IV, fixed, 95% CI)	0.07 (−0.29 to 0.44)
b) Control (unequal dose)	2	106		0.18 (−0.21 to 0.56)
Total	4	220		0.12 (−0.14 to 0.39)
BOTMP-8, postintervention				
a) Comparison equal dose	2	43	SMD (IV, random, 95% CI)	0.82 (0.12 to 1.52)
b) Control (unequal dose)	2	38		1.95 (−1.01 to 4.92)
Total	4	81		1.21 (0.23 to 2.19)
BOTMP-8, 3 to 6 months postintervention				
a) Comparison equal dose	2	43	SMD (IV, random, 95% CI)	0.88 (−0.28 to 2.04)
b) Control (unequal dose)	2	38		4.14 (−4.07 to 12.34)
Total	4	81		1.61 (0.02 to 3.20)
AHA, postintervention				
a) Comparison equal dose	2	104	SMD (IV, random, 95% CI)	−0.04 (−0.42 to 0.35)
b) Control (unequal dose)	4	123		0.13 (−0.39 to 0.66)
Total	6	127		0.07 (−0.23 to 0.37)
AHA, 6 months postintervention				
a) Comparison equal dose	2	100	SMD (IV, random, 95% CI)	−0.09 (−0.48 to 0.30)
b) Control (unequal dose)	2	84		0.10 (−0.72 to 0.92)
Total	4	184		0.02 (−0.34 to 0.37)
COPM-performance, postintervention				
a) Comparison equal dose	2	79	SMD (IV, fixed, 95% CI)	−0.13 (−0.58 to 0.31)
b) Control (unequal dose)	2	84		0.05 (−0.38 to 0.48)
Total	4	163		−0.04 (−0.35 to 0.27)
COPM-satisfaction, postintervention				
a) Comparison equal dose	2	79	SMD (IV, fixed, 95% CI)	−0.24 (−0.68 to 0.20)
b) Control (unequal dose)	2	84		−0.03 (−0.46 to 0.39)
Total	4	163		−0.13 (−0.44 to 0.18)

BOTMP-8, Bruininks-Oseretsky Test of Motor Proficiency subtest 8; FSS, Functional Skills Scale; GAS, Goal Attainment Scale; IV, .

extent of change that would be considered clinically meaningful.[8,18,32] There remains a large treatment effect of BoNT-A and OT compared with OT alone on achieving individualized outcomes, which was sustained at 6 to 8 months postintervention. Intramuscular injections of BoNT-A to the UL is an approach that targets body structure and function; however, the accompanying OT focuses on activity-based outcomes. OT differed in intensity, frequency, duration, and content across studies; however, many studies reported goal-directed training as a component of intervention.[14–20,24] This finding reinforces that activity-based therapy focusing on goals identified as important by children and their caregivers is an integral aspect of UL intervention. Results of this review concur with the findings of a large Cochrane systematic review of UL BoNT-A[61] that OT alone is beneficial and BoNT-A provides a supplementary effect to enhance UL and individualized outcomes.

There remains limited evidence to support the use of NDT in clinical practice. This approach aims to remediate impairments and facilitate more normal movement patterns[62] with the assumption of translation into improved

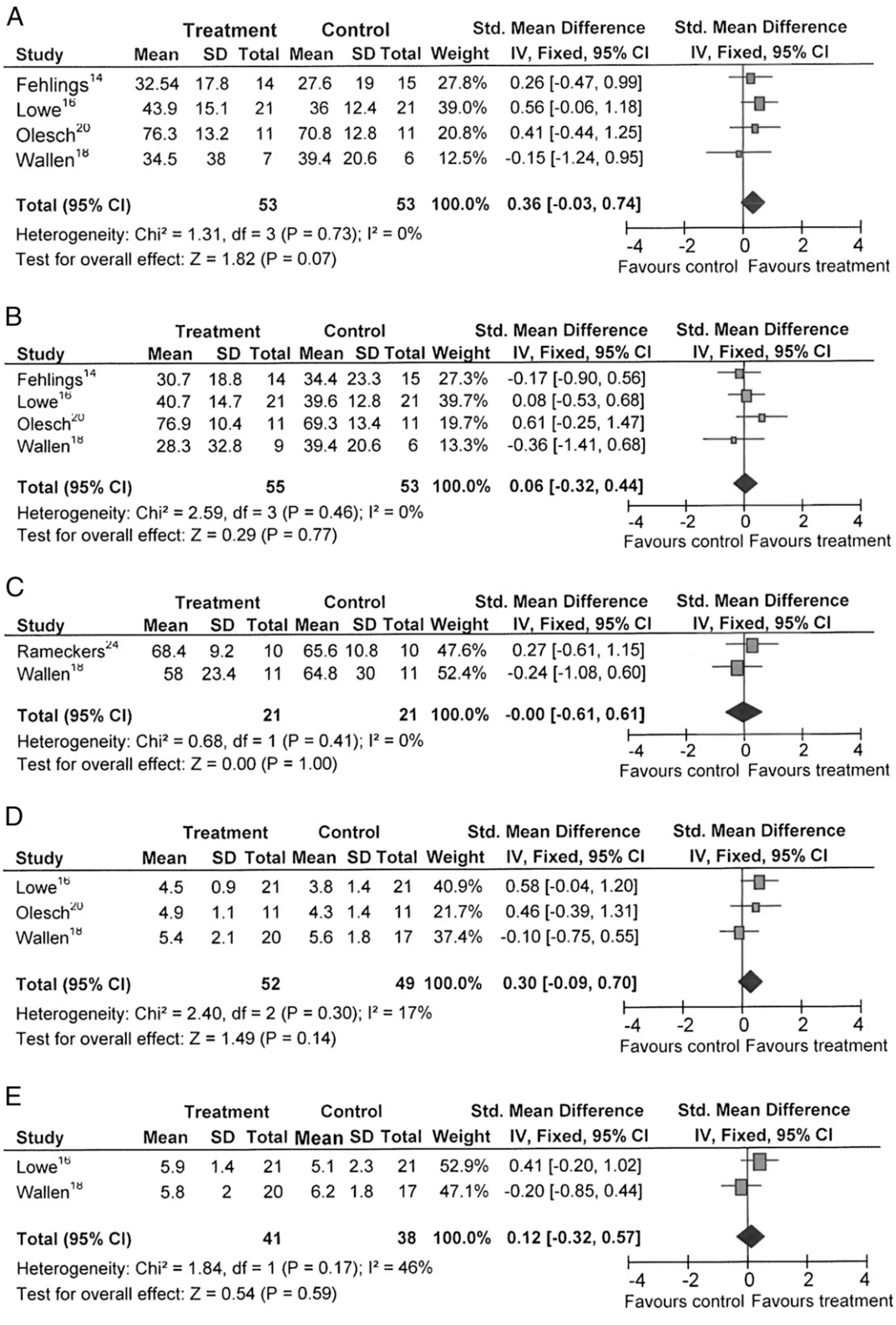
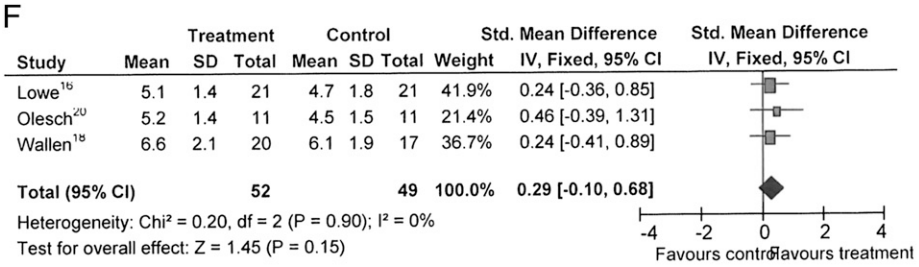


FIGURE 2

Meta-analyses of the effect of BoNT-A and OT versus OT alone. A and B, Results of UL quality of movement postintervention and 6 to 8 months postintervention, respectively: QUEST. C, Results of UL quality of movement 6 months postintervention: Melbourne Assessment. D and E, Results of individualized outcomes postintervention and 6 months postintervention, respectively: COPM performance. F and G, Results of individualized outcomes postintervention and 6 months postintervention, respectively: COPM satisfaction. H and I, Results of individualized outcomes postintervention and 6 to 9 months postintervention, respectively: GAS. J and K, Results of self-care outcomes postintervention and 6 months postintervention, respectively: PEDI Self-Care Functional Skills Scale. GAS, Goal Attainment Scale; IV, inverse variance; PEDI, Pediatric Evaluation of Disability Inventory.

F



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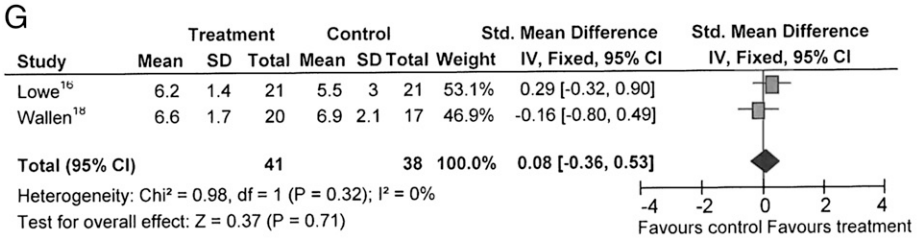

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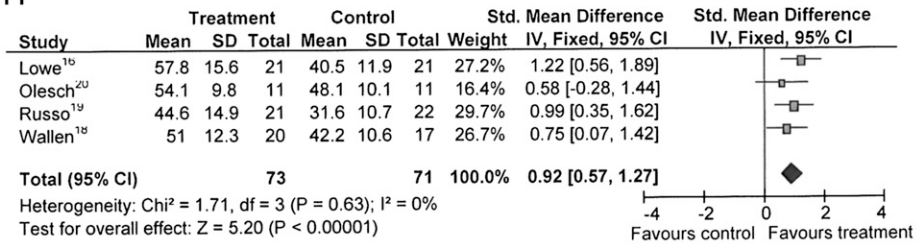

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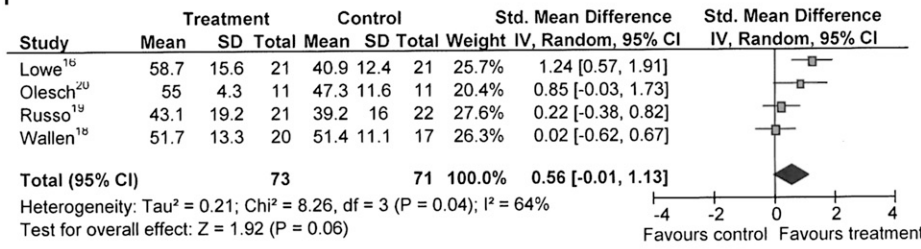

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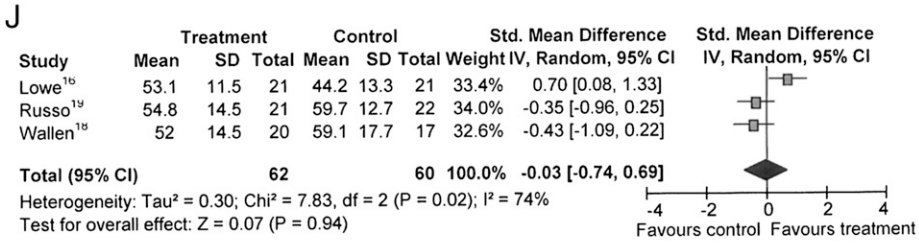

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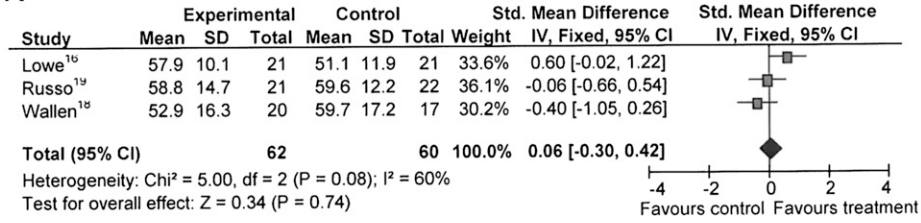

FIGURE 2
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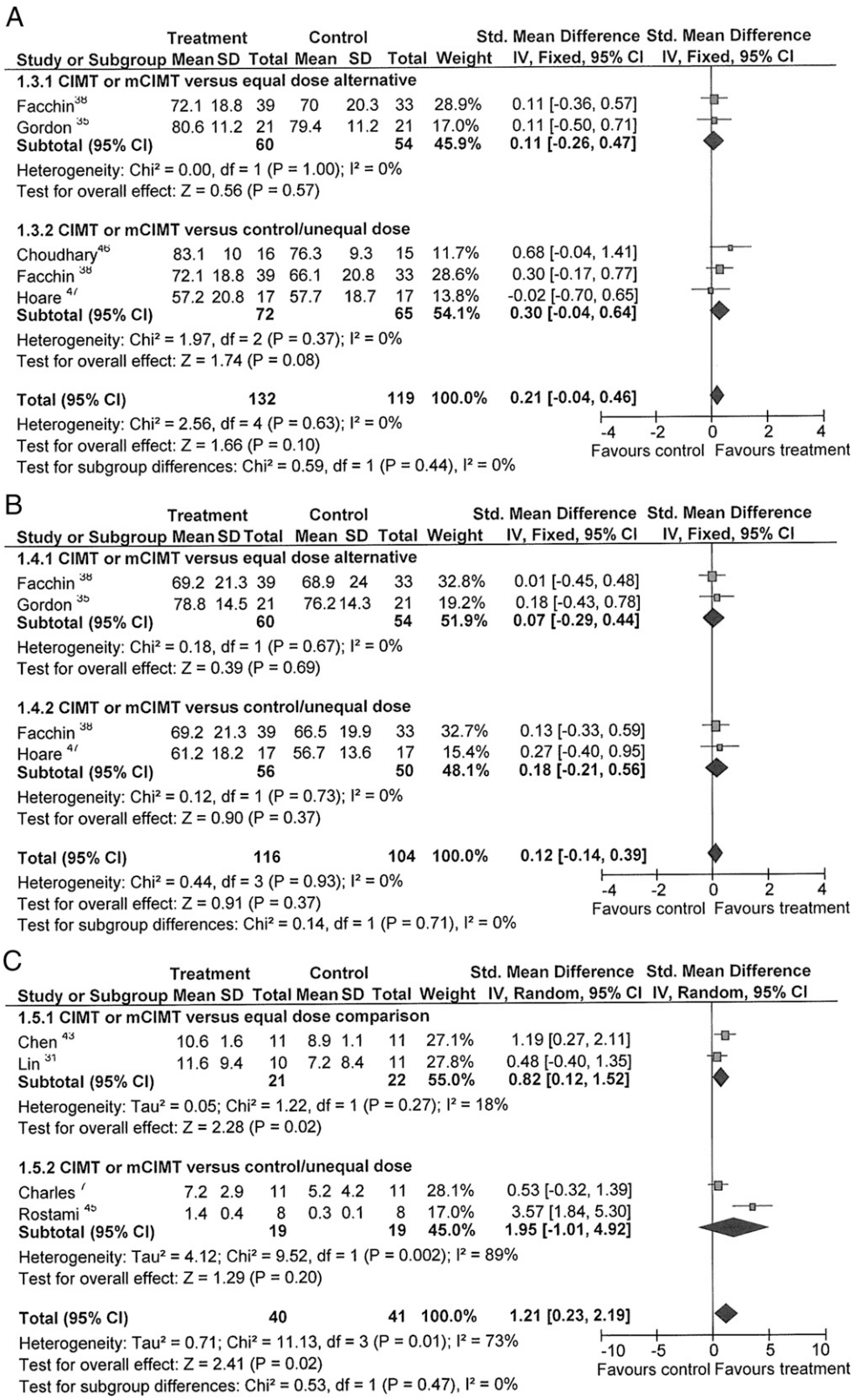
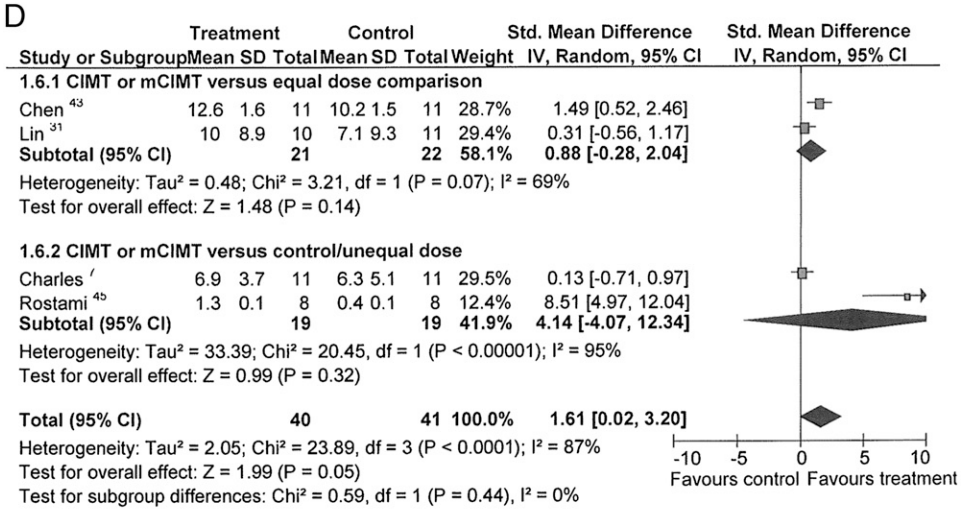


FIGURE 3

Meta-analyses of the effect of CIMT or mCIMT versus control (unequal dose) or comparison (equal dose). A and B, Results of grasp postintervention and 6 months postintervention, respectively: QUEST Grasp Domain. C and D, Results of unimanual and bimanual movement efficiency postintervention and 3 to 6 months postintervention, respectively: BOTMP subtest 8. E and F, Results of bimanual performance postintervention and 6 months postintervention, respectively: AHA. G, Results of individualized outcomes postintervention: COPM performance. H, Results of individualized outcomes postintervention: COPM satisfaction. BOTMP, Bruininks-Oseretsky Test of Motor Proficiency; IV, inverse variance.

D



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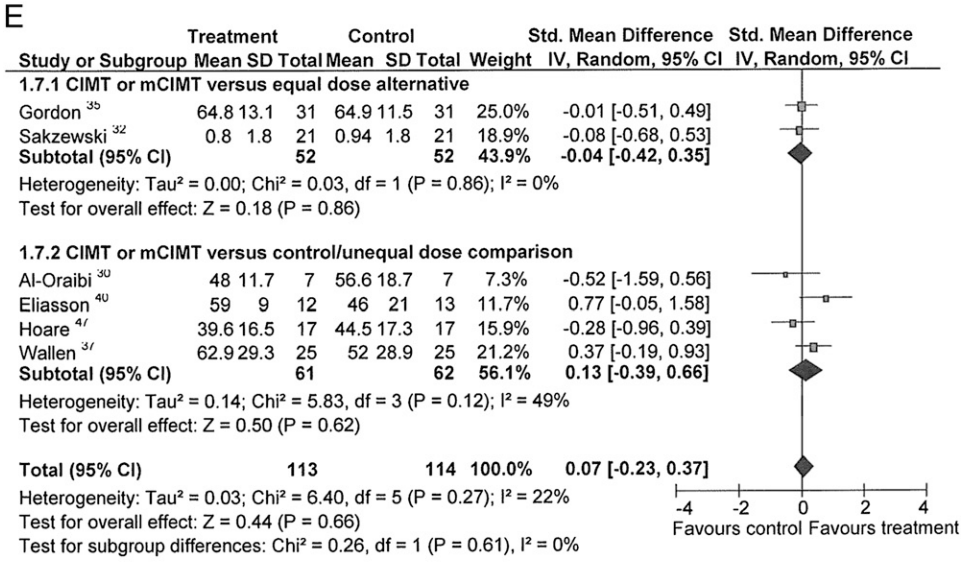

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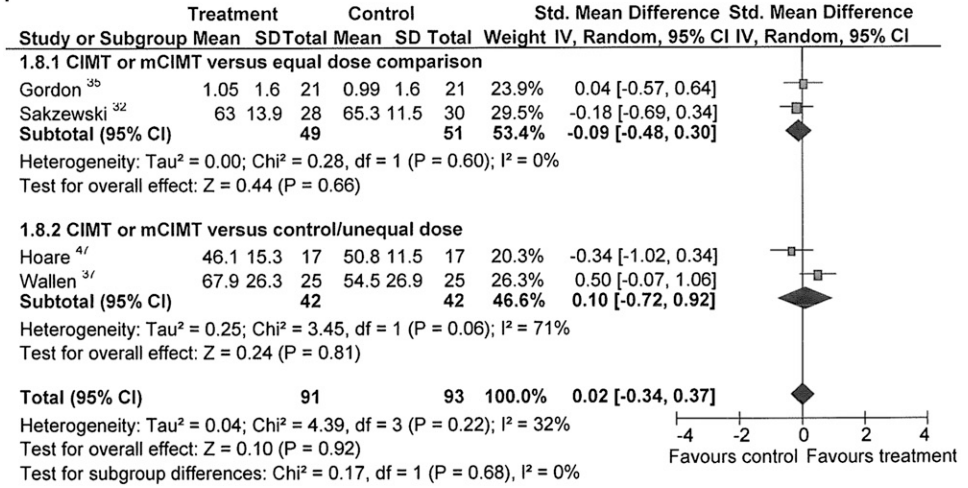

FIGURE 3
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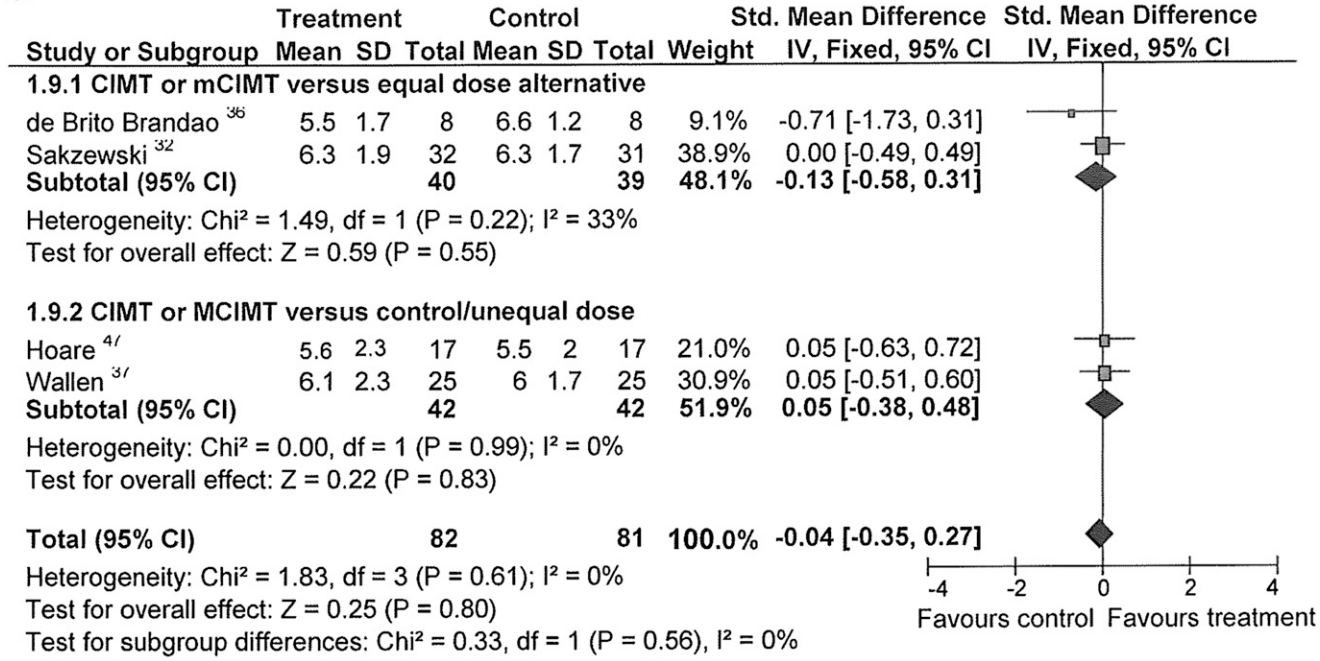

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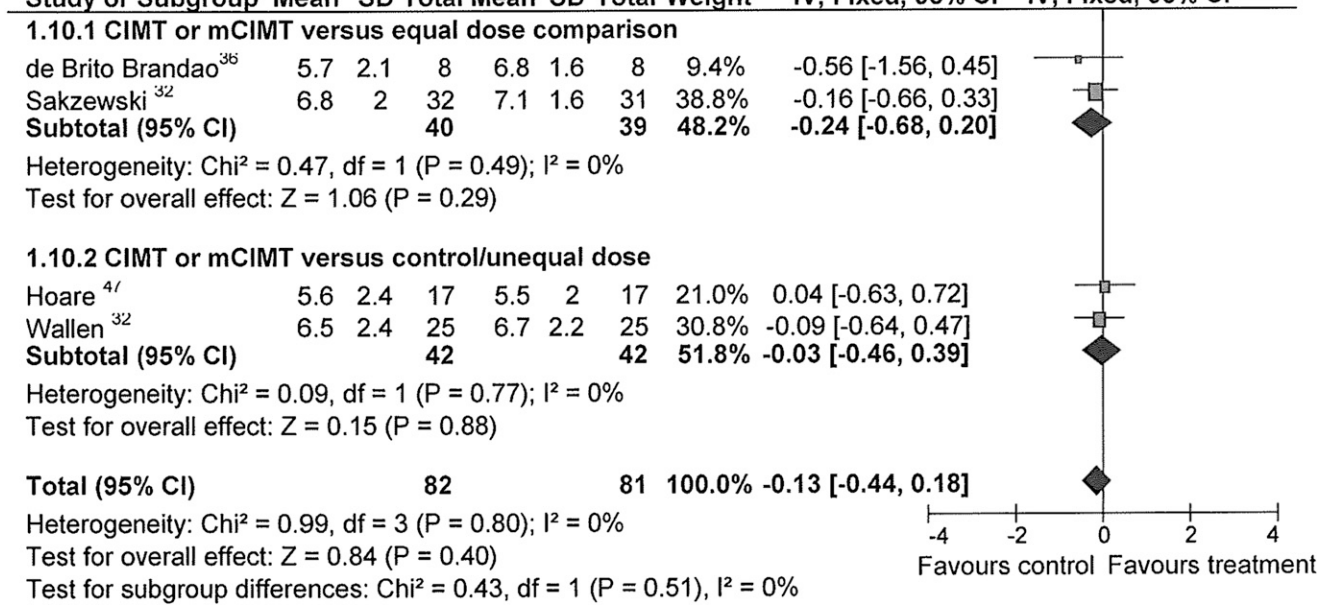

FIGURE 3
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TABLE 6 Summary of Results of Studies Reporting on Individualized Outcomes

Study	Outcome	Timing, wk	*n*	Treatment, Mean (±SD)	*n*	Control, Mean (±SD)	SMD (95% CI)	*P*
NDT								
Law et al[13]	COPM-P	16	26	6.5 (1.6)	24	5.7 (1.4)	0.53 (−0.04 to 1.09)	
		40		6.1 (1.6)		5.5 (1.7)	0.36 (−0.20 to 0.92)	
	COPM-S	16	26	7.1 (1.9)	24	5.8 (1.8)	0.70 (0.12 to 1.26)	.02
		40		6.7 (1.8)		5.8 (1.7)	0.51 (−0.06 to 1.07)	
BoNT-A								
Lowe et al[16]	COPM-P	3	21	4.5 (0.9)	21	3.8 (1.4)	0.59 (−0.03 to 1.20)	
		12		5.3 (1.4)		4.5 (1.4)	0.57 (−0.06 to 1.18)	
		26		5.9 (1.4)		5.1 (2.3)	0.42 (−0.20 to 1.02)	
	COPM-S	3		5.1 (1.4)		4.1 (1.8)	0.62 (−0.01 to 1.21)	
		12		5.8 (1.4)		4.7 (1.8)	0.68 (0.05 to 1.29)	.03
		26		6.2 (1.4)		5.4 (3)	0.34 (−0.27 to 0.94)	
	GAS-family	3		36.1 (10.1)		27.1 (6.4)	1.06 (0.40 to 1.69)	.00
		12		42 (10.1)		34.1 (9.2)	0.82 (0.17 to 1.43)	.01
		26		46.8 (10.5)		40.1 (13.3)	0.56 (−0.07 to 1.16)	
	GAS-ther	3		57.8 (13.8)		40.5 (11.9)	0.94 (0.29 to 1.56)	.00
		12		61 (17.4)		46.8 (12.4)	0.62 (−0.01 to 1.23)	.05
		26		58.7 (15.6)		49.9 (12.4)	1.29 (0.63 to 1.96)	.00
Kawamura et al[17]	GAS	12	18	52.5 (9.0)	21	49.9 (10.5)	0.26 (−0.38 to 0.90)	
Wallen et al[18] (a)[a]	COPM-P	12	19	5.6 (1.4)	15	4.4 (1.3)	0.66 (−0.03 to 1.36)	.05
		26		5.9 (1.8)		5.1 (1.6)	0.46 (−0.26 to 1.17)	
	COPM-S	12		6.5 (1.7)		5.4 (1.9)	0.11 (−0.57 to 0.79)	
		26		6.8 (1.8)		6.3 (1.9)	0.27 (−0.44 to 0.97)	
	GAS	12		42.3 (13.7)		32.9 (10.3)	0.79 (0.08 to 1.49)	.02
		26		52.5 (13.3)		40.6 (12.0)	0.93 (0.20 to 1.62)	.01
Wallen et al[18] (b)[b]	COPM-P	12	20	5.4 (2.1)	17	5.6 (1.8)	−0.1 (−0.75 to 0.55)	
		26		5.8 (2)		6.2 (1.8)	−0.21 (−0.85 to 0.44)	
	COPM-S	12		6.6 (2.1)		6.1 (1.9)	0.24 (−0.41 to 0.89)	
		26		6.6 (1.7)		6.9 (2.1)	−0.16 (−0.80 to 0.49)	
	GAS	12		51 (12.3)		42.2 (10.6)	0.98 (0.29 to 1.66)	.00
		26		51.7 (13.3)		51.4 (11.1)	0.02 (−0.62 to 0.67)	
Russo et al[19]	GAS	12	21	44.6 (14.9)	22	31.6 (10.7)	0.97 (0.34 to 1.60)	.00
		26		43.1 (19.2)		39.2 (16.0)	0.22 (−0.38 to 0.82)	
Olesch et al[20]	COPM-P	16	11	4.9 (1.4)	11	4.3 (1.4)	0.48 (−0.39 to 131)	
		32		4.9 (1.5)		4.4 (1.4)	0.34 (−0.51 to 1.17)	
		48		4.3 (1.4)		4.3 (1.4)	0.58 (−0.30 to 1.41)	
	COPM-S	16		5.2 (1.4)		4.5 (1.5)	0.48 (−0.38 to 1.31)	
		32		5.3 (1.7)		4.5 (1.7)	0.47 (−0.39 to 1.30)	
		48		5.2 (1.8)		4.3 (1.5)	0.54 (−0.33 to 1.30)	
	GAS	16		54.1 (9.8)		48.1 (10.1)	0.60 (−0.27 to 1.43)	
		32		55 (4.3)		47.3 (11.6)	0.88 (−0.03 to 1.72)	.05
		48		54.9 (9.5)		50 (7.1)	0.58 (−0.29 to 1.41)	
mCIMT								
Sakzewski et al[32]	COPM-P	3	32	6.3 (1.9)	31	6.3 (1.5)	0.0 (−0.49 to 0.49)	
		26		6.1 (2.0)		6.2 (1.7)	−0.05 (−0.57 to 0.46)	
		52		6.5 (2.1)		6.6 (1.7)	−0.05 (−0.57 to 0.47)	
	COPM-S	3		6.8 (2.0)		7.0 (1.6)	−0.11 (−0.60 to 0.39)	
		26		6.8 (2.2)		6.8 (1.6)	0.00 (−0.51 to 0.51)	
		52		7.2 (2.0)		6.9 (2.1)	0.15 (−0.38 to 0.67)	
Wallen et al[37]	COPM-P	10	25	6.1 (2.3)	25	6.0 (1.7)	0.05 (−0.51 to 0.60)	
		26		6.8 (1.9)		6.8 (1.5)	0.00 (−0.55 to 0.55)	
	COPM-S	10		6.5 (2.4)		6.7 (2.2)	−0.09 (−0.64 to 0.47)	
		26		7.2 (2.1)		7.2 (2.0)	0.00 (−0.55 to 0.55)	
	GAS	10		0.5 (0.9)		0.5 (0.8)	0.00 (−0.55 to 0.55)	
		26		0.9 (0.9)		0.8 (0.8)	0.12 (−0.44 to 0.67)	
Gordon et al[35] and de Brito Brandão et al[36]	GAS	0.3	21	51(7.9)	21	59.1 (8.4)	−0.99 (−1.61 to −0.33)	.00
		4		54.5 (7.2)		61.3 (7.2)	−0.94 (−1.56 to −0.29)	.00
		26		59 (7.7)		63.8 (7.5)	−0.63 (−1.24 to 0.00)	.05
	COPM-P	0.1	8	5.5 (1.7)		6.6 (1.2)	−0.71 (−1.68 to 0.34)	
	COPM-S	0.1		5.7 (2.1)		6.8 (1.6)	−0.59 (−1.56 to 0.44)	

TABLE 6 Continued

Study	Outcome	Timing, wk	*n*	Treatment, Mean (±SD)	*n*	Control, Mean (±SD)	SMD (95% CI)	*P*
Hoare et al[47]	COPM-P	4	17	3.1 (1.7)	17	3.4 (1.6)	−0.16 (−0.83 to 0.51)	
		12		5.6 (2.3)		5.5 (2.0)	0.07 (−0.60 to 0.75)	
		26		5.5 (2.3)		5.6 (1.8)	−0.06 (−0.73 to 0.61)	
	COPM-S	4		3.2 (1.9)		3.6 (1.8)	−0.21 (−0.88 to 0.47)	
		12		5.6 (2.5)		5.5 (2.0)	0.00 (−0.67 to 0.68)	
		26		5.6 (2.6)		5.8 (2.2)	−0.09 (−0.76 to 0.58)	
Hybrid model: combined mCIMT and bimanual training								
Aarts et al[8]	COPM-P	9	28	6.5 (1.0)	24	4.6 (1.4)	1.59 (0.91 to 2.21)	.00
		17		6.5 (0.9)		4.7 (1.4)	1.57 (0.91 to 2.18)	.00
	COPM-S	9		7.4 (1.2)		5.3 (1.2)	1.75 (1.07 to 2.38)	.00
		17		7.3 (1.2)		5.5 (1.2)	1.50 (0.85 to 2.11)	.00
	ABILHAND	9		28.4 (5.9)		23.7 (6.0)	0.79 (0.2 to 1.36)	.01
		17		28.9 (5.2)		24.4 (6.6)	0.77 (0.18 to 1.33)	.01
Other UL interventions								
Novak et al[51] (a)[c]	COPM-P	4	12	4.3 (1.8)	12	3.4 (1.5)	0.54 (−0.29 to 1.34)	
		8		5.4 (1.9)		3.4 (1.5)	1.17 (0.27 to 1.99)	.01
	COPM-S	4		4.4 (2.3)		3.6 (2.0)	0.37 (−0.45 to 1.16)	
		8		5.4 (2.2)		3.6 (2.0)	0.86 (−0.01 to 1.66)	.05
	GAS	4		51.5 (13.9)		26.0 (2.1)	2.57 (1.41 to 3.54)	.00
		8		60.7 (15.6)		26.0 (2.1)	3.12 (1.84 to 4.18)	.00
Novak et al[51] (b)[d]	COPM-P	4	11	4.8 (2.2)	12	3.4 (1.5)	0.75 (−0.12 to 1.57)	
		8		5.9 (2.2)		3.4 (1.5)	1.34 (0.39 to 2.19)	.00
	COPM-S	4		5.1 (1.8)		3.6 (2.0)	0.79 (−0.09 to 1.60)	
		8		6.1 (1.9)		3.6 (2.0)	1.28 (0.34 to 2.13)	.01
	GAS	4		47.1 (11.6)		26.0 (2.1)	2.59 (1.41 to 3.59)	.00
		8		64.3 (15.4)		26.0 (2.1)	3.57 (2.15 to 4.73)	.00
Elliott et al[52]	GAS	12	8	53 (5)	8	35 (6.8)	3.02 (1.46 to 4.24)	.00

ABILHAND, ; GAS, Goal Attainment Scale; P, performance; S, satisfaction; ther, therapist.

[a] Wallen et al (a) BoNT-A and OT versus control.

[b] Wallen et al (b) BoNT-A and OT versus OT.

[c] Novak et al (a) 8 week OT Home program versus control.

[d] Novak et al (b) 4 week OT Home program versus control.

activity performance. No further investigations of NDT have been conducted since the previous systematic review; however, a recent trial compared context-focused with child-focused therapy for children with CP.[53] Child-focused therapy targeted impairments and included some elements of NDT, such as facilitation of normal movement patterns and postural control using physical handling techniques provided through practice of functional activities.[53] When compared with a context-focused intervention, which involved goal-directed, activity-based training, task, and environmental modifications, there were no significant differences between the interventions.

Adjunctive therapies in combination with direct therapy were reported for splinting and functional electrical stimulation. Splints are generally not used as a stand-alone intervention but as an adjunct to other UL approaches. Two broad aims of splinting include prevention of contractures and deformities and enhancing UL function through better positioning of the arm and hand. A number of BoNT-A studies have included static night splints as a component of UL intervention.[15,16,21,22,24] One study evaluated the additional effect of static night splints accompanying BoNT-A and OT and found improved quality of UL movement at 6 months postintervention compared with BoNT-A and OT alone.[21] This was a small study with poor methodologic quality, and findings need to be replicated in an adequately powered trial. The use of functional electrical stimulation as part of an integrated UL therapy program including BoNT-A, OT, and night splint was evaluated in a small trial and found a supplementary effect on UL function.[22] The sample size of this study was small and methodologic quality poor; therefore, results should be viewed cautiously. Splinting aimed to improve UL function was evaluated in 1 small study of dynamic lycra UL splints worn for 3 months and accompanied by goal-directed training.[52] Findings showed improved goal attainment compared with a control group.

Two new interventions, mirror therapy and action observation training, have been investigated first in adult stroke rehabilitation and then in small pilot trials for children with unilateral CP.[54,56] Mirror therapy creates a visual illusion of a functional impaired arm using a mirror reflection of the unimpaired arm. Movements of the unimpaired limb are performed while watching its reflection in a mirror that shows the

TABLE 7 Summary of Results of Studies Reporting on Self-Care Outcomes

Study	Outcome	Timing, wk	*n*	Treatment, Mean (±SD)	*n*	Control, Mean (±SD)	SMD (95% CI)	*P*
BoNT-A								
Fehlings et al[14] (change scores)	PEDI Self-Care	4	14	2.6 (6.9)	15	−1.5 (4.1)	0.73 (−0.05 to 1.46)	
	FSS	12		2.8 (3.7)		1.1 (4.1)	0.43 (−0.31 to 1.16)	
		26		5.5 (4.5)		3.3 (6.1)	0.41 (−0.34 to 1.13)	
Lowe et al[16]	PEDI Self-Care	4	21	53.1 (11.5)	21	44.2 (13.3)	0.72 (0.08 to 1.33)	
	FSS	12		55.8 (11.5)		48.3 (11.0)	0.67 (0.03 to 1.27)	
		26		57.9 (10.1)		51.1 (11.9)	0.62 (−0.01 to 1.22)	
Kawamura et al[17]	PEDI Self-Care	4	18	64.9 (12.5)	21	66.4 (15.3)	−0.11 (−0.73 to 0.53)	
	FSS	12		66.8 (12.1)		63.0 (11.6)	0.32 (−0.32 to 0.95)	
Wallen et al[18] (a)	PEDI Self-Care	12	20	66.7 (12.7)	15	55.0 (18.2)	0.87 (0.16 to 1.57)	.01
	FSS	24		63.2 (15.5)		58.8 (21.7)	2.61 (1.64 to 3.46)	.00
Wallen et al[18] (b)	PEDI Self-Care	12	20	52.0 (14.5)	17	59.1 (17.7)	−0.46 (−1.11 to 0.02)	
	FSS	24		52.9 (16.3)		59.7 (17.2)	−0.41 (−1.05 to 0.25)	
Russo et al[19]	AMPS-motor	12	21	0.5 (0.70)	22	0.7 (0.6)	−0.31 (−0.91 to 0.30)	
		26		0.7 (1.0)		0.8 (0.5)	−0.19 (−0.79 to 0.41)	
	AMPS-process	12		0.4 (0.9)		0.5 (0.7)	−0.18 (−0.78 to 0.42)	
		26		0.5 (1.0)		0.7 (0.7)	−0.21 (−0.81 to 0.39)	
	PEDI Self-Care	12		54.8 (14.5)		59.7 (12.7)	−0.36 (−0.96 to 0.25)	
	FSS	26		58.8 (14.7)		59.6 (12.2)	−0.06 (−0.66 to 0.54)	
mCIMT								
Hoare et al[47]	PEDI Self-Care	4	17	34.2 (10.0)	17	40.6 (9.8)	−0.64 (−1.31 to 0.06)	
	FSS	12		41.3 (12.7)		45.1 (10.8)	−0.32 (−0.99 to 0.36)	
		26		42.1 (11.0)		49.2 (14.7)	−0.55 (−1.22 to 0.15)	
de Brito Brandão et al[36]	PEDI Self-Care	0.1	8	60.1 (6.1)	8	63.5 (5.0)	−0.60 (−1.57 to 0.43)	
	FSS							
Hybrid model: combined mCIMT and bimanual training								
de Brito Brandão et al[9]	PEDI Self-Care	1	8	74.5 (9.9)	7	69.2 (6.3)	0.63 (−0.44 to 1.63)	
	FSS	4		77.4 (9.3)		70.8 (7.2)	0.78 (−0.31 to 1.78)	
Forced-use therapy								
Sung et al[48]	WeeFIM Self-Care	1	18	25.4 (5.8)	13	21.2 (8.7)	0.87 (0.00 to 1.68)	.05
Other UL interventions								
Law et al[53]	PEDI Self-Care	26	71	51.5 (18.2)	57	49.1 (15.0)	0.14 (−0.21 to 0.49)	
	FSS	38		51.9 (18.7)		51.8 (17.8)	0.01 (−0.34 to 0.35)	

AMPS, Assessment of Motor and Process Skills; FSS, Functional Skills Scale; WeeFIM, Functional Independence Measure for Children.

image of the unimpaired limb superimposed over the impaired limb. Studies of adults poststroke have shown improved UL motor function and reduced pain after mirror therapy.[63] Action observation training involves watching a motor action performed by another person, followed by execution of that motor action, and is believed to tap into the mirror neuron system.[64] There is some evidence in adults poststroke that action observation training leads to improved UL motor function.[65,66] The 2 pilot trials of mirror therapy[54] and action observation training[56] in children with unilateral CP showed some preliminary benefits on UL function; however, these approaches should continue to be viewed as experimental until further larger trials can be performed.

A number of potential limitations exist with the current evidence for UL interventions. Generally, studies continue to report small sample sizes. Compared with the previous review, there is improved consistency in outcome measures. The AHA[67] (measure of bimanual performance) has been increasingly used in mCIMT, cCIMT, HABIT, and hybrid models, although the impact of BoNT-A and OT on bimanual performance remains unclear. Bimanual performance should be seen as a key outcome of UL intervention, reflecting that most functional tasks in daily life are bimanual in nature. The importance of bimanual performance was confirmed across a range of UL interventions that highlighted that most goals identified by caregivers and children were bimanual self-care, leisure, and productivity related.[18,20,33,35,37,51] The AHA is a valid and reliable performance measure for children with unilateral CP,[67] has demonstrated sensitivity to change in clinical trials,[32,35,40,47] and is a useful clinical tool for program planning.[40,47] As a measure of performance, the AHA is more reflective of actual real-world use of the impaired UL as an assisting hand in bimanual tasks as opposed to unimanual capacity measures that target the child's best effort in a standardized environment. Greater measurement of individualized outcomes has occurred across UL intervention trials, which is important given the heterogeneity of the population, and reflects a greater focus on goal-directed training.

RESEARCH IMPLICATIONS

Despite the rapid increase in evaluation of UL therapies for children with unilateral CP, a number of key questions remain:

1. What is the optimum mode and dose of UL training to accompany intramuscular injections of BoNT-A and how does intervention impact bimanual performance?
2. What are the most effective interventions to improve UL function in infants <1 year of age?
3. What is the critical threshold dose of intervention and is there a dose-age relationship?
4. Is there additional benefit of intensive short-duration interventions versus distributed models of care and does the context of therapy delivery (home, school, clinic, community) impact outcomes?
5. What are the characteristics of children who achieve clinically meaningful outcomes after intervention? Individual studies have attempted to elucidate predictors of a clinically meaningful response in post hoc analyses[7,26,47,50,68]; however, findings have not been consistent. An individual patient data meta-analysis may allow greater exploration of subgroups and unique child and intervention factors that might lead to clinically meaningful outcomes.

CONCLUSIONS

This review highlighted a growing body of evidence for a variety of UL interventions in children with unilateral CP. Synthesizing results of these studies provides therapists with some clear clinical guidelines: (1) therapy should be goal-directed, working on the goals identified by children and their caregivers; (2) goals should be measured objectively; (3) contemporary motor learning approaches that use activity-based therapy should be used; (4) the UL outcomes of therapy should be measured objectively by using reliable and valid outcome measures; and (5) intervention should provide an adequate dose of therapy. Although the exact critical threshold dose of therapy remains unclear, it is certainly more than current standard care. The evidence allows flexibility in how intervention is delivered, due to the variations in models of intervention that have been investigated. Therapists augmenting their direct therapy with home programs should be guided by the work of Novak.[51]

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Address correspondence to Leanne Sakzewski, PhD, BOcc Thy, Queensland Cerebral Palsy and Rehabilitation Research Centre, Level 7, Block 6, Royal Brisbane Hospital, Herston Rd, Herston QLD 4029, Australia. E-mail: l.sakzewski1@uq.edu.au

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