A systematic review of interventions for children with cerebral palsy: state of the evidence

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AIM The aim of this study was to describe systematically the best available intervention evidence for children with cerebral palsy (CP).
METHOD This study was a systematic review of systematic reviews. The following databases were searched: CINAHL, Cochrane Library, DARE, EMBASE, Google Scholar MEDLINE, OTSeeker, PEDro, PsycBITE, PsycINFO, and speechBITE. Two independent reviewers determined whether studies met the inclusion criteria. These were that (1) the study was a systematic review or the next best available; (2) it was a medical/allied health intervention; and (3) that more than 25% of participants were children with CP. Interventions were coded using the Oxford Levels of Evidence; GRADE; Evidence Alert Traffic Light; and the International Classification of Function, Disability and Health.
RESULTS Overall, 166 articles met the inclusion criteria (74% systematic reviews) across 64 discrete interventions seeking 131 outcomes. Of the outcomes assessed, 16% (21 out of 131) were graded 'do it' (green go); 58% (76 out of 131) 'probably do it' (yellow measure); 20% (26 out of 131) 'probably do not do it' (yellow measure); and 6% (8 out of 131) 'do not do it' (red stop). Green interventions included anticonvulsants, bimanual training, botulinum toxin, bisphosphonates, casting, constraint-induced movement therapy, context-focused therapy, diazepam, fitness training, goal-directed training, hip surveillance, home programmes, occupational therapy after botulinum toxin, pressure care, and selective dorsal rhizotomy. Most (70%) evidence for intervention was lower level (yellow) while 6% was ineffective (red).
INTERPRETATION Evidence supports 15 green light interventions. All yellow light interventions should be accompanied by a sensitive outcome measure to monitor progress and red light interventions should be discontinued since alternatives exist.

Thirty to 40% of interventions have no reported evidence-based and, alarmingly, another 20% of interventions provided are ineffectual, unnecessary, or harmful.[1] The gap between research and practice has been well documented in systematic reviews[1] across multiple diagnoses, specialties, and countries. Surveys confirm that, unfortunately, the research–practice gap occurs within the cerebral palsy (CP) field to the same degree.[2,3] This gap exists despite numerous systematic reviews providing guidance about what does and does not work for children with CP. When clinicians want to help, families expect effective interventions, and the health system depends upon cost-effective services, the provision of ineffectual interventions is illogical. In view of this, why is there such variable uptake of best available evidence within real clinical practice?

In the last decade, the CP evidence base has rapidly expanded, providing clinicians and families with the possibility of newer, safer, and more effective interventions. Orthopaedic surgery and movement normalization were once the mainstays of intervention, but localized antispasticity medications and motor learning interventions have gained increased popularity.[4,5] Thus, the sheer volume of research published makes it hard for clinicians to keep up to date.[6] Systematic reviews seek to provide evidence summaries, but, in spite of this, clinicians find it difficult to interpret review findings and stay abreast of these syntheses.[7] Furthermore, the introduction of new and sometimes competing effective interventions increases the complexity of clinical reasoning required by clinicians, who are primarily motivated to improve outcomes for children.[8]

In the last 10 years, the field has adopted the World Health Organization's International Classification of Functioning, Disability and Health (ICF),[9] which has redefined the way clinicians understand CP and think about inter-

vention options. From an ICF perspective, CP impacts on a person's 'functioning', (inclusive of body structures [e.g. limbs], body functions [e.g. intellectual function], activities [e.g. walking], and participation [e.g. playing sport]), which in turn may cause 'disabilities', such as impairments, activity limitations, and participation restrictions. Moreover, each person with CP lives within a personalized environment and thus their context also contributes to determining their independence, comprising personal factors (e.g. motivation) and environmental factors (e.g. architectural accessibility).[9,10] Thus, there are many potential problems a child with CP may face and seek intervention for. The field has chosen a philosophical shift away from almost exclusively redressing physical impairments underlying functional problems to adopting an additional focus on maximizing children's environment, their independence in daily activities, and their community participation.[11] Furthermore, clinicians applying the recommended goal-based approach seek to choose interventions guided by what would best help the family achieve their goals.[12–14] Couple these philosophical preferences with widespread barriers to research implementation (such as limited time, insufficient library access, limited research appraisal skills, attitudinal blocks to research, and differing patient preferences), and there is no assurance that children with CP will receive evidence-based interventions.[1,15,16]

The aim of this paper was to describe systematically the best available evidence for CP interventions using the GRADE[17] system and to complement these findings with the Evidence Alert Traffic Light System[18] in order to provide knowledge translation guidance to clinicians about what to do. The purpose of rating the whole CP intervention evidence base within the one paper was to provide clinicians, managers, and policy-makers with a 'helicopter' view of best available intervention evidence that could be used to (1) inform decision-making by succinctly describing current evidence about CP interventions across the wide span of disciplines involved in care; (2) rapidly aid comparative clinical decision-making about similar interventions; and (3) provide a comprehensive resource that could be used by knowledge brokers to help prioritize the creation of knowledge translation tools to promote evidence implementation.[19]

METHOD
Study design
A systematic review of systematic reviews (i.e. the highest level of CP intervention research evidence available) was conducted in order to provide an overview of the current state of CP intervention evidence. Systematic reviews were preferentially sought since reviews provide a summary of large bodies of evidence and reviews help to explain differences among studies. Moreover, reviews limit bias which assists clinicians, managers, and policy-makers with decision-making about current best available evidence.[20] However, for interventions for which no systematic reviews existed, lower levels of evidence were included to illuminate the current state of the evidence.

What this paper adds
• Of 64 discrete CP interventions, 24% are proven to be effective.
• 70% have uncertain effects and routine outcome measurement is necessary.
• 6% are proven to be ineffective.
• Effective interventions reflect current neuroscience and pharmacological knowledge.
• All effective interventions worked at only one level of the ICF.

Search strategy
Our review was carried out using a protocol based upon recommendations from the Cochrane Collaboration and PRISMA statements.[21,22] Relevant articles were identified by searching the CINAHL (1983–2012); Cochrane Database of Systematic Reviews (1993–2013; www.cochrane.org); Database of Reviews of Effectiveness (DARE); EMBASE (1980–2012); ERIC; Google Scholar; MEDLINE (1956–2012); OTSeeker (www.otseeker.com); Physiotherapy Evidence Database (PEDro [www.pedro.fhs.usyd.edu.au]); Psychological database for Brain Impairment Treatment Efficacy (PsycBITE [www.psycbite.com]); PsycINFO (1935–2012); PubMED; and Speech Pathology Database for Best Interventions and Treatment Efficacy (speechBITE [www.speechbite.com]). Searches were supplemented by hand searching. The search of published studies was performed in July and August 2011 and updated in December 2012. Interventions and keywords for investigation were identified using (1) contributing authors' knowledge of the field; (2) internationally recognized CP websites such as the American Academy of Cerebral Palsy and Developmental Medicine (www.aacpdm.org), *CanChild* (www.canchild.ca), the Cerebral Palsy Alliance (www.cerebralpalsy.org.au), Cincinnati Children's Hospital (www.cincinnatichildrens.org), Karolinksa Insitutet (www.ki.se), NetChild (www.netchild.nl), NeuroDevNet (www.neurodevnet.ca), and Reaching for the Stars (www.reachingforthestars.org); and (3) the top 20 hits in Google using the search term 'cerebral palsy' as an indicator of popular subject matter.

Electronic databases were searched with EBSCO host software using PICOs [patient/problem, intervention, comparison, and outcome] search terms. The full search strategy is available from the authors on request.

Inclusion criteria
Published studies about intervention for children with CP fulfilling criteria under the headings below were included.

Type of study
First, studies of level 1 evidence (systematic reviews), rated using the Oxford 2011 Levels of Evidence were preferentially sought.[23] The Oxford 2011 Levels of Evidence for treatment benefits include level 1, a systematic review of randomized trials or *n*-of-1 trials; level 2, a randomized trial or observational study with dramatic effect; level 3, a non-randomized controlled cohort/follow-up study; level 4, a case series, case–control study, or a historically controlled study; and level 5, mechanism-based reasoning.

Evidence of Oxford levels 2 to 4 were included only if (1) level 1 evidence did not exist on the topic and then the next best available highest level of evidence was included; or if (2) level 2 randomized controlled trial(s) had been published since the latest systematic review, which substantially changed knowledge about the topic.

Second, retrieved bodies of evidence were coded using the GRADE[17] system and Evidence Alert Traffic Light System[18] using two independent raters, with 100% agreement reached. The GRADE[17] system was chosen because it is a criterion standard evidence-grading tool and is endorsed by the World Health Organization. Definitions of the GRADE terms appear in the notes to Table I and a full description of panel rating processes are available from www.gradeworkinggroup.org/publications/JCE_series (retrieved 8 March 2013). Notably, the GRADE system rates both (1) the quality of the evidence (randomized trials, high; observational studies, low; and other levels of evidence, very low, but it is worth mentioning that high-quality evidence is downgraded if methodological flaws exist and low-quality evidence is upgraded if high and certain effect sizes exist [e.g. population-based CP register data])[17] and (2) the strength of the recommendation for use, which weighs up trade-offs between the benefits and harms of using the intervention, whereby a panel considers (a) the methodological quality of the evidence supporting estimates of likely benefit and likely risk; (b) inconvenience; (c) the importance of the outcome that the treatment prevents; (d) the magnitude of the treatment effect; (e) the precision of the estimate of the treatment effect; (f) the risks associated with therapy; (g) the burdens of therapy; (h) the costs; and (i) the varying values.[17] The GRADE methodology means that sometimes bodies of evidence may be assigned a strong recommendation even when the quality of the evidence is low. This is either because there is a high likelihood of harm from no intervention (e.g. anticonvulsants to prevent seizures or ulcer prevention pressure care) or because the treatment has a low effect size and is expensive to provide, but a safe, more effective, cost-comparable alternative exists (e.g. phenol vs botulinum toxin A; or neurodevelopmental therapy [NDT] vs motor learning). The Evidence Alert Traffic Light System[18] was chosen because it is a GRADE-complementary knowledge translation tool, designed to assist clinicians to obtain easily readable, clinically useful answers within minutes.[6] The Evidence Alert also provides a simple, common language between clinicians, families, managers, and funders, based upon three-level colour coding that recommends a course of action for implementation of the evidence within clinical practice. The Evidence Alert System[18] has been shown to increase by threefold clinicians' reading habits about CP research.[24] Figure 1 describes the GRADE system and the Evidence Alert System and their relationship to each other. Table I shows the included studies, best evidence levels grades and traffic light classification.[25–185]

Where multiple systematic reviews existed and newer level 1 to 2 evidence superseded the findings of earlier level 1 evidence, the grades were assigned based on the most recent high-quality evidence.

Types of intervention
Studies were included if they involved the provision of and intervention by either a medical practitioner or allied health professional.

Types of participants
Studies were included if they explicitly involved human participants and more than 25% of the participants were children with CP.

Studies were excluded from the review if (1) they were diagnostic studies, prognostic studies, or interventions aimed at preventing CP (e.g. magnesium sulphate[186] and hypothermia[187]); (2) they provided lower levels of evidence, unless no systematic review had been published; (3) participants were adults, although if a study predominantly (>75%) studied children but included a small proportion of young adults (<25%) the paper was included; (4) they reviewed generic prophylaxis interventions (e.g. good parenting, standard neonatal care for all infants, i.e. not CP-specific interventions); (5) they reviewed a whole discipline, not individual interventions (e.g. physiotherapy, occupational therapy, speech pathology); (6) they were considered alternative and complementary interventions with no published evidence; (7) a second publication of the same study published the same results; and (8) they were unpublished or not peer reviewed.

Data abstraction
A data abstraction sheet based on the Cochrane's recommendations[21] was developed. Abstracts identified from searches were screened by two independent raters (CP research experts and knowledge brokers) to determine their eligibility for further review. Abstracts were retained for full review if they met the inclusion criteria or if more information was required from the full text to confirm that the study met all the eligibility criteria. Two independent reviewers then reviewed full-text versions of all retained articles and all additional articles identified by hand searching. Full-text articles were retained if they met inclusion criteria. Agreement on inclusion and exclusion assignment of the full-text articles was unanimous. Data extracted from included studies comprised the authors and date of the study; the type and purpose of the intervention implemented; the study design; the original authors' conclusions about efficacy across study outcomes; and the original authors' conclusions on strength of evidence (based on their assessment of whether there was no evidence of benefit, qualified support, or strong support). For lower level evidence, risk of bias was assessed using the Cochrane criteria.

The data extracted from each included study were summarized, tabulated, and assigned a level of evidence rating

Table I: Included studies, best available evidence levels, grades and traffic lights

	Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE Quality of evidence	GRADE Strength of recommendation	Traffic light action
1	Acupuncture: electro-stimulation to scalp and body via needles and manual pressure	Improved gross motor function (A)	Zhang[25]	Insufficient evidence	1	Low	Weak +	Yellow MEASURE
2	Alcohol: muscular injections to induce chemical denervation for treating local spasticity	Reduce muscle spasticity locally via injections (BS)	Delgado[26]	Insufficient evidence to support, but BoNT-A exists as a highly effective alternative – therefore probably do not use alcohol unless BoNT-A total dose limitations in play	1	N/A	Weak −	Yellow MEASURE
3	Alternative and augmentative communication: technology alternatives to verbal speech, e.g. communication boards, speech generating devices	Improved general communication skills (A)	Pennington[27]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow I MEASURE
		Improved communication skills of pre-school children (A)	Branson[28]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
		Improved communication skills of conversational partners (P)	Pennington[29]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
		Enhanced supplementation of verbal speech (A)	Hanson[30] Millar[31]	Lower-quality supporting evidence	1 1	Very low	Weak +	Yellow MEASURE
4	Animal-assisted therapy: service animals to provide companionship and assist with independence, e.g. seizure first aid, door opening, crossing roads	Improved socialization and mood; reduced stress, anxiety and loneliness; and improved leisure (BS and P)	Muñoz Lasa[32]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
		Improved independence via service dogs (P)	Winkle[33]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
5	Anticonvulsants: medications to prevent seizures	Improved seizure control (BS)	—	No evidence in CP. Since high quality evidence exists in non-CP populations and there are high risks of adverse events from uncontrolled seizures therefore – do use anticonvulsants	–	N/A	Strong +	Green GO
6	Assistive technology: equipment or devices to improve independence e.g. walking frames, wheelchairs, adapted computer access	Improved independence in activities of daily living (A and P)	Wilson[34]	Lower-quality supporting evidence	2	Low	Weak +	Yellow MEASURE
		Improved computer access via a switch or key guard (A)	Davies[35]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
		Improved independence in early mobility via powered wheelchairs (A and P)	Jones[36] Livingstone[37]	Lower-quality supporting evidence	2 1	Low	Weak +	Yellow MEASURE
		Improved participation in education, communication and play via alternative computer access (P)	Chantry[38] Sandlund[39]	Lower-quality supporting evidence	1 1	Very low	Weak +	Yellow MEASURE
		Improved function via robotic training or virtual reality (A)	Laufer[40] Parsons[41] Sandlund[39] Snider[42] Wang[43]	Lower-quality supporting evidence	1 1 1 1	Very low	Weak +	Yellow MEASURE
		Improved transfers via a hoist (A)	Jung[44]	Insufficient evidence	1	Very low	Weak +	Yellow MEASURE
		Improved weight bearing and bone mineral density via a standing frame (BS)	Pin[45]	Insufficient evidence	1	Low	Weak +	Yellow MEASURE
		Improved sleep positioning via a sleep system (BS)	Wynn[46]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
		Reduced carer burden (E)	Nicolson[47]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
7	Baclofen (oral): antispasticity medication	Reduced spasticity (BS)	Delagado[26]	Lower-quality supporting evidence	1	Low	Weak +	Yellow MEASURE

Table I: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE Quality of evidence	GRADE Strength of recommendation	Traffic light action
8 Behaviour therapy: positive behaviour support, behavioural interventions, and positive parenting	Improved child behaviour (from the Stepping Stones Triple P Programme) (A)	Roberts[48] Sanders[49]	Effective, but low CP numbers were included in the study samples and publication bias existed	2 2	Low	Weak +	Yellow MEASURE
	Improved parenting skills (E)	Whittingham[50]	Insufficient evidence	1	Very low	Weak +	Yellow MEASURE
9 Bimanual training: repetitive task training in the use of two hands together	Improved hand function, i.e. bilateral hand use for children with hemiplegia (A)	Gordon[51] Sakzewski[4] Sakzewski[52]	Effective. Equal effectiveness to constraint-induced movement therapy	2 1 2	High	Strong +	Green GO
10 Biofeedback: electronic feedback about muscle activity to teach voluntary control	Improved muscle activation and active range of motion (BS)	Dursun[53]	Effective if combined with other treatments	2	Low	Weak +	Yellow MEASURE
	Improved walking (A)	Dursun[53]	Insufficient evidence	2	Low	Weak +	Yellow MEASURE
	Improved hand function (A)	Bloom[54]	Lower-quality supporting evidence	4	Very low	Weak +	Yellow MEASURE
11 Bisphosphonates: medication to suppress bone reabsorption to treat osteoporosis	Improved bone mineral density (BS)	Fehlings[55] Hough[56]	Effective. Small RCTs suggest a positive effect and there are high risks of adverse events from no treatment	1 1	Moderate	Strong +	Green GO
12 Botulinum toxin (BoNT-A): medication injected into overactive spastic muscles to locally block spasticity	Reduced lower limb muscle spasticity (BS)	Ade-Hall[57] Albavera-Hernandez[58] Boyd[59] Heinen[60] Koog[61] Lukban[62] Love[63] Mulligan[64]	Effective and safe	1 1 1 1 1 1 1 1	High	Strong +	Green GO
	Reduced upper limb muscle spasticity (BS)	Fehlings[65] Reeuwijk[66] Wasiak[67]	Insufficient evidence. Note: function was preferentially measured over spasticity reduction in high quality studies. Since the drug is highly effective in lower limb muscles, we expect comparable results – therefore do use BoNT-A	1 1 1	Moderate	Strong +	Green GO
	Reduced hypertonia of the neck muscles (BS)	Novak[68]	Insufficient evidence. Since high-quality evidence supports tone reduction in primary dystonia (non-CP populations), we expect similar results – therefore probably do use BoNT-A	1	N/A	Weak +	Yellow MEASURE
	Improved walking function (A)	Koog[61] Love[63] Ryll[69]	Probably effective in combination with physiotherapy therefore do use	1 1 1	Moderate	Strong +	Green GO
	Improved hand function and performance of functional hand activities (A)	Boyd[59] Fehlings[65] Hoare[70] Hoare[71]	Effective in combination with occupational therapy	1 1 1 1	High	Strong +	Green GO
	Reduced pain (BS)	Rawicki[72]	Insufficient evidence	1	Very low	Weak +	Yellow MEASURE
	Reduced drooling (BS)	Lim[73] Reddihough[74] Walshe[75]	Effective short term and given the adverse social outcomes from no treatment – do use	1 1 1	Moderate	Strong +	Green GO

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE Quality of evidence	GRADE Strength of recommendation	Traffic light action
13 Casting: Plaster casts applied to limbs to (a) stretch muscles for muscle lengthening, i.e. contracture reduction casts changed regularly; or (b) reduce spasticity	Improved passive range of motion of the lower limbs (BS)	Autti-Ramo[76] Blackmore[77] Effgen[78] Katalinic[79]	Effective. Gains in ankle range of motion are very small but are potentially clinically meaningful for children that need more dorsiflexion to walk, therefore – do use	1 1 1 1	Low	Strong +	Green GO
	Improved passive range of motion of the upper limbs (BS)	Autti-Ramo[76] Lannin[80] Teplicky[81]	Insufficient evidence	1 1 1	Low	Weak +	Yellow MEASURE
	Improved function (A)	Autti-Ramo[76] Blackmore[77] Effgen[78] Katalinic[79]	Insufficient evidence	1 1 1 1	Low	Weak −	Yellow MEASURE
	Augmented effects of BoNT (BS)	Blackmore[77]	Effective but gains are small	1	Low	Weak +	Green GO
	Reduced muscle spasticity (BS)	Katalinic[79] Teplicky[82]	Insufficient evidence. Newer understandings of spasticity indicate a 'local' intervention will not improve a 'central' condition – therefore probably do not use casting for spasticity reduction	1 1	Low	Weak −	Yellow MEASURE
14 Coaching parents: emotional support, information exchange and a structured process of tutoring parenting behaviours	Improved parenting skills and coping (E)	Graham[82]	Insufficient evidence. More research needed with stronger designs	4	Very low	Weak +	Yellow MEASURE
15 Cognitive behaviour therapy (CBT): identifying unhelpful thoughts and behaviours and teaching cognitive restructuring and self-management of constructive thinking and actions	Improved depression, anxiety, sleep, attention, behaviour and enuresis (BS)	—	No evidence in CP. Since high-quality evidence supports CBT in non-CP populations – therefore probably do use CBT	–	N/A	Weak +	Yellow MEASURE
16 Communication training: training communication partners to effectively communicate, e.g. Interaction Training; Hanen; It Takes Two to Talk	Improved interaction between children and their parents (P)	Pennington[29] Pennington[83]	Insufficient evidence	1 1	Very low	Weak +	Yellow MEASURE
17 Conductive education (CE): a Hungarian educational classroom-based approach to teaching movement using rhythmic intention, routines and groups	Improved 'orthofunction' (response to biological and social demands) (BS)	Darrah[84] Tuersley-Dixon[85]	Conflicting evidence. Majority of studies show no difference to no treatment	1 1	Low	Weak −	Yellow MEASURE
	Improved performance of functional activities (A)	Darrah[84] Tuersley-Dixon[85]	Conflicting evidence. Majority of studies show no difference to no treatment	1 1	Low	Weak −	Yellow MEASURE
	Improved cognition (BS)	Tuersley-Dixon[85]	Conflicting evidence. Majority of studies show no difference to no treatment	1	Low	Weak −	Yellow MEASURE
18 Constraint-induced movement therapy (CIMT): constraining the dominant hand in a mitt or cast, to enable intensive training of the hemiplegic hand	Improved hand function of the affected hand for children with hemiplegia (A)	Boyd[59] Hoare[86] Huang[87] Nascimento[88] Sakzewski[4]	Effective. Even more RCTs have been published after the included reviews confirming effectiveness	1 1 1 1 1	Moderate	Strong +	Green GO
19 Context-focused therapy: changing the task or the environment (but not the child) to promote successful task performance	Improved function (A)	Law[89]	Effective. Note: a single rigorous RCT shows equal effectiveness to child-focused therapy	2	High	Strong +	Green GO
20 Counselling (parents): fostering understanding of how life problems lead to distress, relationship breakdown and mental health issues, to improve communication and interpersonal skills	Improved parental coping and mental health (E)	—	No evidence in CP. No published research evidence, opinion papers existed	–	N/A	Weak +	Yellow MEASURE
	Improved parental coping via parent to parent support (E)	Palit[90]	Insufficient evidence	4	Very low	Weak +	Yellow MEASURE

Table I: Continued

	Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE Quality of evidence	GRADE Strength of recommendation	Traffic light action
21	Cranial osteopathy: palpation using small movements to ease musculoskeletal strain and treat the central nervous system	Improved mobility, quality of life and general health (A and P)	Wyatt[91]	Ineffective. Note: a single rigorous RCT shows no benefit when compared with no treatment	2	High	Strong −	Red STOP
22	Dantrolene: antispasticity medication	Reduce spasticity (generalized) (BS)	Delgado[26]	Insufficient evidence	1	Low	Weak −	Yellow MEASURE
23	Diazepam: antispasticity medication	Reduce spasticity (generalized) (BS)	Delgado[26]	Effective short term, therefore – do use	1	Moderate	Strong +	Green GO
24	Dysphagia management: promoting safe swallowing by changing food textures, sitting position, oral motor skills and using oral appliances and equipment	Improved safety of swallow via thickened fluids i.e. less aspiration (BS)	Snider[92]	Lower-quality supporting evidence	1	Low	Weak +	Yellow MEASURE
		Improved safety of swallow via upright positioning, i.e. less aspiration (BS)	Snider[92]	Conflicting evidence	1	Low	Weak +	Yellow MEASURE
25	Early intervention (EI): therapy and early education to promote acquisition of milestones, via group or individual stimulus	Improved motor outcomes (BS and A)	Blauw-Hospers[93] Blauw Hospers[94] Turnbull[95] Ziviani[96]	Evidence supports general stimulation, developmental approaches and parent coaching programmes. Gains are superior to NDT or traditional physiotherapy	1 1 1 1	Moderate	Weak +	Yellow MEASURE
		Improved cognitive outcomes (BS)	Blauw-Hospers[93] Blauw Hospers[94] Turnbull[95] Ziviani[96]	High quality evidence supports EI in non-CP populations. Moderate evidence supports EI program memes for at risk pre-term infants, aimed at mimicking the intrauterine environment	1 1 1	Low	Weak +	Yellow MEASURE
26	Electrical stimulation (ES, NMES, FES): electrical stimulation of a muscle through a skin electrode to induce passive muscle contractions for strengthening or motor activation	Improved gait parameters (BS)	Cauraugh[97] Wright[97] Kerr[98] Scianni[99] Wright[97]	Insufficient evidence. Effective in laboratory, unknown effectiveness in the community	1 1 1 1	Low	Weak +	Yellow MEASURE
		Improved muscle strength (BS)		Lower-quality supporting evidence	1	Moderate	Weak +	Yellow MEASURE
		Augmented effects of Botulinum toxin (BS)	Lannin[100] Wright[101]	Conflicting evidence. More evidence needed	1 1	Low	Weak +	Yellow MEASURE
27	Fitness training: planned structured activities involving repeated movement of skeletal muscles that result in energy expenditure to improve or maintain levels of physical fitness	Improved aerobic fitness (BS)	Butler[102] Rogers[103] Verschuren[102]	Effective short term and only in those that have sufficient motor skills to undertake aerobic training. No carryover when training stops. Therefore do use but only in the right patient and plan to continue the programme long term	1 1 1	Moderate	Strong +	Green GO
		Improved function and participation (A and P)	Butler[102] Rogers[103] Verschure n[102]	Insufficient evidence. Aerobic fitness does not appear to translate to activity and participation gains	1 1	Moderate	Weak −	Yellow MEASURE
28	Fundoplication (including Nissen and laparoscopic; gastric plication): surgical procedure to strengthen the barrier to acid reflux, e.g. by wrapping the fundus around the oesophagus	Reduction of gastro-oesophageal reflux (BS)	Vernon-Roberts[103]	No CP-specific evidence	1	N/A	Weak +	Yellow MEASURE

Table I: Continued

	Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	Quality of evidence	Strength of recommendation	Traffic light action
						GRADE		
29	Gastrostomy: surgical placement of a non-oral feeding tube to prevent or reverse growth failure, or prevent aspiration pneumonia, e.g. percutaneous endoscopic gastrostomy (PEG), jejunostomy	Improved growth and weight (BS)	Arrowsmith[104] Kong[105] Samson-Fang[106] Sleigh[107,108] Sullivan[109] Sullivan[110] Vernon-Roberts[111]	Adverse events occur	3 3 1 1 3 3 4	Very low	Weak +	Yellow MEASURE
30	Goal-directed training/functional training: task specific practice of child-set goal-based activities using a motor learning approach	Improved gross motor function (A)	Ketelaar[112] Lowing[113]	Effective. Some probability of bias within included studies	2 3	Low	Weak +	Yellow MEASURE
		Improved hand function (A)	Novak[13] Sakzewski[52] Wallen[14]	Effective. Can be delivered via a home programme or used in combination with CIMT and bimanual training. Low probability of bias within included studies	2 2 2	High	Strong +	Green GO
		Improved self-care (A)	Novak[13] Wallen[14]	Effective. Low probability of bias within included studies	2 2	High	Strong +	Green GO
31	Hand surgery: surgery to improve hand function and alignment	Improved thumb-in-palm posture (BS)	Smeulders[114]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
32	Hip surgery: orthopaedic surgery to improve musculoskeletal alignment of the hip	Reduced hip subluxation via soft tissue surgery (adductor release) (BS)	Stott[115]	Most studies were uncontrolled	1	Very low	Weak +	Yellow MEASURE
		Reduced hip subluxation via bony surgery (BS)	Brunner[116] Huh[117]	Studies were retrospective and uncontrolled	4 4	Very low	Weak +	Yellow MEASURE
33	Hip surveillance: active surveillance and treatment for hip joint integrity to prevent hip dislocation	Reduced hip dislocation and need for orthopaedic surgery (BS)	Gordon[118]	Hip surveillance is a regular assessment process so as the right treatments can be provided in a timely manner, as such the studies were appropriately designed as observational studies not RCTs. Do use as there are substantive adverse events from no surveillance	1	Moderate	Strong +	Green GO
34	Hippotherapy: therapeutic horse riding to practice balance and symmetry	Improved hip and trunk symmetry and stability (BS)	Snider[119] Sterba[120] Zadnikar[121]	Effective	1 1 1	Low	Weak +	Yellow MEASURE
		Improved gross motor function (A)	Whalen[122]	Effective. Larger studies needed	1	Low	Weak +	Yellow MEASURE
		Improved participation (P)	Davis[123]	Insufficient evidence. Sensitive measures required in future studies	2	Moderate	Weak –	Yellow MEASURE
35	Home programmes: therapeutic practice of goal-based tasks by the child, led by the parent and supported by the therapist, in the home environment	Improved performance of functional activities (A)	Novak[124] Novak[13]	Effective. Note: a single rigorous RCT shows effectiveness, with a low probability of bias	1 2	Moderate	Strong +	Green GO
		Improved participation (P)	Novak[13]	Insufficient evidence. Sensitive measures required in future studies	2	Moderate	Weak –	Yellow MEASURE
36	Hydrotherapy: aquatic-based exercises	Improved vitals and gross motor function (BS and A)	Chrysagis[125] Getz[126] Gorter[127]	Lower-quality supporting evidence	2 1 1	Low	Weak +	Yellow MEASURE
37	Hyperbaric oxygen (HBO): inhaled 100% oxygen inside a pressurized hyperbaric chamber	Improved performance of functional activities (A)	Collet[128] McDonagh[129]	Ineffective. Adverse events can also occur	2 1	High	Strong –	Red STOP

Table I: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	Quality of evidence	Strength of recommendation	Traffic light action
						GRADE	
38 Intrathecal baclofen (ITB): antispasticity medication delivered directly to the spinal cord via a pump surgically implanted within the abdomen	Reduced lower limb spasticity (BS)	Butler[130] Creedon[131] Dan[132] Delgado[26] Kolaski[133]	Predominantly low-quality supporting evidence. The size of the gains varies between studies	1 1 1 1	Low	Weak +	Yellow MEASURE
	Reduced upper limb spasticity (BS)	Butler[130] Creedon[131] Dan[132] Delgado[26] Kolaski[133]	Insufficient evidence. The effect on upper limb is less than for the lower limb and some authors question whether ITB is clinically worthwhile for the purposes of reducing upper limb spasticity	1 1 1 1	Low	Weak –	Yellow MEASURE
	Reduced dystonia (BS)	Albanese[134] Butler[130]	Lower-quality supporting evidence	1 1	Very low	Weak +	Yellow MEASURE
	Improved function and health related quality of life (A, P and PF)	Hoving[135] Hoving[136] Kolaski[133]	Lower-quality supporting evidence	2 2 1	Low	Weak +	Yellow MEASURE
	Improved walking ability in ambulant children (A)	Pin[137]	Insufficient evidence. Some children with CP improve but many experience adverse events including inability to walk	1	Very low	Weak –	Yellow MEASURE
39 Massage: therapeutic stroking and circular motions applied by a massage therapist to relieve pain and tension	Reduced pain (BS)	Hernandez-Reif[138] Nilsson[139]	Conflicting evidence	2 2	Low	Weak +	Yellow MEASURE
	Reduced spasticity (BS)	Alizad[140] Hernandez-Reif[138]	Conflicting evidence	2 2	Low	Weak +	Yellow MEASURE
	Improved function (A)	Hernandez-Reif[138]	Conflicting evidence	2	Low	Weak +	Yellow MEASURE
40 Neurodevelopmental therapy (NDT, Bobath): direct, passive handling and guidance to optimise function	Normalized movement (BS)	Brown[141] Butler[142]	Ineffective. No gains superior to other treatments	1 1	Low	Strong –	Red STOP
	Prevent contracture development (BS)	Brown[141] Butler[142]	Ineffective because immediate gains in range of motion observed within the session do not carry over	1 1	Low	Strong –	Red STOP
	Improved function (A)	Brown[141] Butler[142] Martin[143]	Conflicting systematic review evidence. Early reviews suggested no benefits. The more recent review included one new trial suggesting possible benefit of higher doses of NDT compared with lower doses of NDT; however, this is not a conventional method for establishing treatment efficacy and should be interpreted with caution. Other evidence shows that motor learning produces superior functional gains to NDT	1 1	Low	Weak –	Yellow MEASURE
41 Occupational therapy after BoNT: improved hand use via CIMT, goal-directed training, strength training and functional hand splints. improved symptom management via casting and immobilisation splints	Enhanced social emotional and cognitive skills (BS and PF)	Brown[141] Butler[142]	Ineffective. No evidence to support claim	1 1	Low	Strong –	Red STOP
	Improved goal achievement of upper limb activities (A)	Boyd[59] Fehlings[65] Hoare[70] Hoare[71] Lannin[99]	Effective	1 1 1 1 1	High	Strong +	Green GO

Table I: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	Quality of evidence	Strength of recommendation	Traffic light action
					GRADE		
42 Oral motor treatment: sensory stimulation to lips, jaw, tongue, soft palate, larynx, and respiratory muscles to influence the oropharyngeal mechanism	Improved verbal speech as a result of non-speech oral motor exercises (BS)	–	No evidence in CP. Insufficient evidence to support or refute in non-CP[200] populations	–	N/A	Weak –	Yellow MEASURE
43 Orthopaedic surgery: surgical prevention or correction of musculoskeletal disorders and associated muscles, joints, and ligaments, e.g. muscle lengthening	Improved safety of swallowing and reduced drooling (BS)	Snider[92] Wilcox[144]	Insufficient evidence	1	Very low	Weak –	Yellow MEASURE
	Correct equinus foot deformity (BS)	Shore[145]	Lower-quality supporting evidence with no superior surgical technique evident. Studies indicated that early surgery was a major risk factor for recurrent equinus deformity	1	Low	Weak +	Yellow MEASURE
44 Orthotics (splints): removable external devices designed to support weak or ineffective joints or muscles	Improved stride length and range of motion via AFOs (BS)	Autti-Ramo[76] Blackmor e[77] Effgen[78] Figueiredo[146] Harris[147] Morris[148] Teplicky[81]	Positive effects on ankle range of motion, gait kinetics and kinematics, but the quality of the evidence is low	1	Very low	Weak +	Yellow MEASURE
	Improved lower limb function (A)	Autti-Ramo[76] Blackmore[77] Effgen[78] Figueiredo[146] Harris[147] Morris[148] Teplicky[81]	Insufficient evidence	1	Very low	Weak –	Yellow MEASURE
	Improved upper limb function (A)	Teplicky[81]	Insufficient evidence	1	Very low	Weak –	Yellow MEASURE
	Prevention of contracture (BS)	Teplicky[81]	High-quality evidence shows ineffective in non-CP populations, but insufficient CP studies to be certain	1	Very low	Weak –	Yellow MEASURE
	Prevention of hip dislocation via hip orthoses and botulinum toxin (BS)	Graham[149]	High-quality evidence shows may slow hip dislocation rate slightly but essentially ineffective for preventing hip dislocation	2	High	Strong –	Red STOP
45 Parent training: educating and coaching parents to change their child's behaviour or skills, plus improve parenting	Improved parenting skills to facilitate child development (E)	Whittingham[50]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
46 Phenol: muscular injections to induce chemical denervation for treating local spasticity	Reduce spasticity locally (BS)	Delgado[26]	No CP studies appraised. Since high-quality evidence supports BoNT-A. However, in clinical care, phenol is sometimes used positively in combination with BoNT-A to enable injection of more muscles groups to remain within safe total dose restrictions	1	N/A	Weak –	Yellow MEASURE
47 Play therapy: play and creative arts to enhance emotional wellbeing and advance play skills	Improved play skills (A)	Redditi Hanzlik[150]	Insufficient evidence	2	Low	Weak +	Yellow MEASURE
	Improved child coping and reduced stress (BS and PF)	–	No evidence in CP	–	N/A	Weak +	Yellow MEASURE
48 Pressure care: prevention of pressure ulcers via good positioning, repositioning, and suitable support surfaces	Reduced ulcer development via high-specification foam mattresses, alternating pressure mattresses, and medical grade sheepskins (BS)	McInnes[151]	Effective. Alternating pressure mattresses more cost-effective than alternating pressure overlays	1	Low	Strong +	Green GO
	Reduced ulcer development from wheelchair seat cushions (BS)	McInnes[151]	Insufficient evidence	1	Low	Weak +	Yellow MEASURE

Table I: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE Quality of evidence	GRADE Strength of recommendation	Traffic light action
49 Respite: temporary caregiving break for parents where the child is usually accommodated outside the home	Improve family functioning and reduce parental stress (E)	Strunk[152]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
50 Seating and positioning: assistive technology that enables a person to sit upright with functional, symmetrical or comfortable posture, to enable function	Improved pulmonary function (BS)	Farley[153] Ryan[154]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
	Improved posture and postural control (BS)	Chung[155] Farley[153] Roxborough[156] Ryan[154]	Insufficient evidence	1	Very low	Weak +	Yellow MEASURE
	Improved hand function (A)	Farley[153] McNamara[157] Ryan[154]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
	Reduced pressure via tilt (BS)	Michael[158]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
51 Selective dorsal rhizotomy (SDR): neurosurgical procedure that selectively severs nerve roots in the spinal cord, to relieve spasticity	Reduced spasticity (BS)	Grunt[159] McLaughlin[160] Steinbok[161]	Effective	1	Moderate	Strong +	Green GO
	Improved gait kinematics (BS)	Grunt[159] McLaughlin[160] Steinbok[161]	Effective	1	Low	Strong +	Green GO
	Improved function and participation (A and P)	Grunt[159] McLaughlin[160] Steinbok[161]	Evidence for improved gross motor function, but no supporting evidence for general activities and participation and this should not be the primary goal for using SDR	1	Very low	Weak +	Yellow MEASURE
52 Sensory integration (SI): therapeutic activities to organize sensation from the body and environment, to facilitate adaptive responses, e.g. hammock swinging	Improved sensory organization (BS)	Vargas[162]	Ineffective. Since meta-analyses of SI compared with no treatment had average effect sizes of 0.03 (for most recent studies)	1	Low	Strong −	Red STOP
	Improved motor skills (A)	Vargas[162]	Ineffective. Since Goal directed training, CIMT or bimanual therapy exist as effective alternatives. Meta-analyses of SI compared to no treatment had average effect sizes of 0.03 (for most recent studies), and 0.09 for SI compared to alternative treatments. Note reviews for non-CP populations excluded	1	Low	Strong −	Red STOP
53 Sensory processing: therapeutic activities to organize more appropriate responsiveness (i.e. not hyper-responsive and not hyporesponsive) to task and environmental demands, including self-regulation	Improved function (A)	–	No evidence in CP. Since performance-based approaches (e.g. CO-OP) are more favourable than impairment-based approaches, e.g. sensory processing (in non-CP populations)	–	N/A	Weak −	Yellow MEASURE
54 Single event multilevel surgery with therapy: multiple simultaneous surgical procedures at different levels of the lower limb to either improve gait or prevent deterioration	Improved long-term functional mobility (A)	McGinley[163]	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
55 Social stories: an individualized book describing a situation, skill, or concept and the relevant social cues, perspectives, and common responses to prepare a child for a social situation	Improved communication and management of emotions and behaviours (A)	Test[164]	Insufficient evidence	1	Very low	Weak +	Yellow MEASURE
56 Solution-focused brief therapy: resource orientated and goal focused approach to generating solutions to life challenges	Reduced parental depression, improved coping and improved parenting skills (E)	–	No evidence in CP. Since low-quality evidence shows emergent effectiveness in non-CP populations[198]	–	N/A	Weak +	Yellow MEASURE

Table I: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE Quality of evidence	GRADE Strength of recommendation	Traffic light action
57 Strength training (resistance): use of progressively more challenging resistance to muscular contraction to build muscle strength and anaerobic endurance	Improved lower limb strength via progressive resistance training (BS)	Dodd[165] Effgen[78] Jeglinsky[166] Martin[143] Mockford[167] Scianni[168] Taylor[169]	Effective short term for improving muscle strength. Improved muscle strength does not carry over to function, other treatment approaches will be needed for functional gains	1 1 1 1 1 1	Low	Weak +	Yellow MEASURE
	Improved upper limb strength via progressive resistance training (BS)	Kim[170]	Effective short term for improving muscle strength	2	Low	Weak +	Yellow MEASURE
	Improved function via progressive resistance training (A)	Scianni[168]	Insufficient evidence	1	Low	Weak −	Yellow MEASURE
	Improved function via functional training using resistance within functional tasks (A)	Martin[143]	Lower-quality supporting evidence	1	Low	Weak +	Yellow MEASURE
58 Stretching: use of an external passive force (e.g. parent) exerted upon the limb to move it into a new and lengthened position	Contracture prevention via manual stretching (BS)	Katalinic[79] Wiart[171]	Ineffective. Comprehensive and robust meta-analysis showed no immediate, or short– to medium-term benefits (<7mo), but, since only a small number of CP studies were included within the review, it is not possible to be certain about this recommendation for CP	1 1	Moderate	Weak −	Yellow MEASURE
	Contracture prevention via splinting or positioning (BS)	Autti-Ramo[76] Pin[45] Teplicky[81]	Insufficient evidence	1 1 1	Low	Weak +	Yellow MEASURE
59 Therasuits: a breathable soft dynamic orthotic full body suit, designed to improve proprioception, reduce reflexes, restore synergies and provide resistance	Improved gross motor function (A)	Alagesan[172] Bailes[173]	Conflicting evidence. One trial suggests positive effect the other suggest no benefits	2 2	Low	Weak −	Yellow MEASURE
60 Tizanidine: antispasticity medication	Reduce spasticity (generalized) (BS)	Delgado[26]	Insufficient evidence	1	Low	Weak +	Yellow MEASURE
61 Treadmill training: walking practice on a treadmill, which includes partial body support	Improved weight bearing (BS)	Zwicker[174]	Lower-quality supporting evidence	1	Low	Weak +	Yellow MEASURE
	Improved functional walking (A)	Damiano[175] Mutlu[176] Willoughby[177] Zwicker[174]	Lower-level supporting evidence. However, overground walking more effective than partial body weight-supported treadmill training	1 1 1	Low	Weak +	Yellow MEASURE
62 Vitamin D (with our without calcium or growth hormones): dietary vitamin supplement for bone density	Improved bone mineral density (BS)	Fehlings[55] Hough[56]	Insufficient evidence	1 1	Low	Weak +	Yellow MEASURE
63 Vojta: therapist applied pressure to defined zones on the body whilst positioned in prone, supine or side lying, where the stimulus leads to automatically and involuntarily complex movement	Improve strength and movement, plus lessen severity of CP (BS)	Brandt[178] d'Avignon[179] Kanda[180] Liu[181] Wu[182] Zhang[183] Zhao[188]	Conflicting evidence. Studies claim to 'cure' early CP, which is not consistent with any of the other literature about CP having no known cure. Also the studies reported high dropout rates due to child distress. Studies have a high probability of bias, e.g. lack of: random sequence generation; concealed allocation, study blinding, psychometrically sound instruments; plus incomplete outcome data collection and selective reporting	2 2 3 2 2 2 2	Very low	Weak −	Yellow MEASURE

Table I: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	Quality of evidence	Strength of recommendation	Traffic light action
						GRADE	
64 Whole-body vibration: assistive technology that transmits low-frequency vibration to the body through a broad contact area of a vibrating surface, e.g. feet in standing, buttocks in sitting, or whole body	Improved strength (BS)	del Pozo-Cruz[185]	Lower-quality supporting evidence in non-CP population, but no effect in CP. Small numbers of CP studies we cannot be certain about this recommendation for CP	1	Very low	Weak –	Yellow MEASURE
	Improved gait (BS and A)	del Pozo-Cruz[185]	Insufficient evidence	1	Very low	Weak –	Yellow MEASURE

Under 'Quality of evidence', 'High' means that further research is very unlikely to change our confidence in the estimate of effect; 'Moderate' means that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; 'Low' means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and 'Very low' means that any estimate of effect is very uncertain.[17] Under 'Strength of recommendation', 'Strong +' means 'do it', indicating a judgement that most well-informed people would make; 'Weak +' means 'probably do it', indicating a judgement that a majority of well-informed people would make but a substantial minority would not; 'Weak –' means 'probably do not do it', indicating a judgement that a majority of well-informed people would make but a substantial minority would not; 'Strong –' means 'do not do it', indicating a judgement that most well-informed people would make.[17] A, activities; BS, body structures and function; P, participation; RCT, randomized controlled trial; E, environmental; PF, personal factors.

using the Oxford Levels of Evidence; a categorization using GRADE; a colour coding scheme using the Evidence Alert Traffic Light system, and an ICF domain (Table I). More specifically, each intervention outcome sought by included study authors was assigned an ICF domain based upon published literature.[176] It has been acknowledged in the literature that ICF coding is notoriously complex to apply since CP is a disability not a disease, and thus direct interventions do not ultimately alter underlying disease processes.[10] To overcome this challenge, we applied ICF codes using CP literature precedents, where the outcome measure within the included trials had been ICF coded by other authoritative researchers.[10] Of note, ICF linking rules typically cluster together (1) body structure and functions; and (2) activities and participation. To prevent loss of findings obscured within aggregated data, we separated activities from participation because we wanted to illuminate whether or not participation outcomes were being achieved. All the data required to answer the study questions were published within the papers, so no contact with authors was necessary.

Ethics and registration
The study did not involve contact with people, so the need for ethical approval was waived by the Cerebral Palsy Alliance's Human Research ethics committee. This systematic review was not registered.

RESULTS
Using the search strategy, 33 485 citations were identified, of which 166 articles met the inclusion criteria for review (Fig. 2).

Participants
For the purpose of this study, participants had CP, which is a complex and heterogeneous condition. We included studies about children with CP of any motor subtype (spastic, dyskinetic, or ataxic), any topography (hemiplegic/unilateral, diplegic/bilateral, or quadriplegic/bilateral), and any functional ability level (Gross Motor Function Classification System [GMFCS][188] levels I to V and Manual Ability Classification System [MACS][189] levels I to V). There was substantial emphasis in the medical literature on interventions to reduce spasticity, the most prevalent motor impairment.[190] There was also a heavy emphasis in the therapy literature on interventions designed to improve motor outcomes consistent with CP being a physical disability. The higher-quality studies defined the child's motor function abilities using the GMFCS and MACS to enable better interpretation of treatment effects taking into account the severity of the disability. However, there was insufficient homogeneity of reporting across studies to enable reporting by GMFCS level, which was our original intended strategy.

Levels of evidence and ICF
High levels of evidence existed in the literature summarizing interventions for children with CP (Table I). Of the
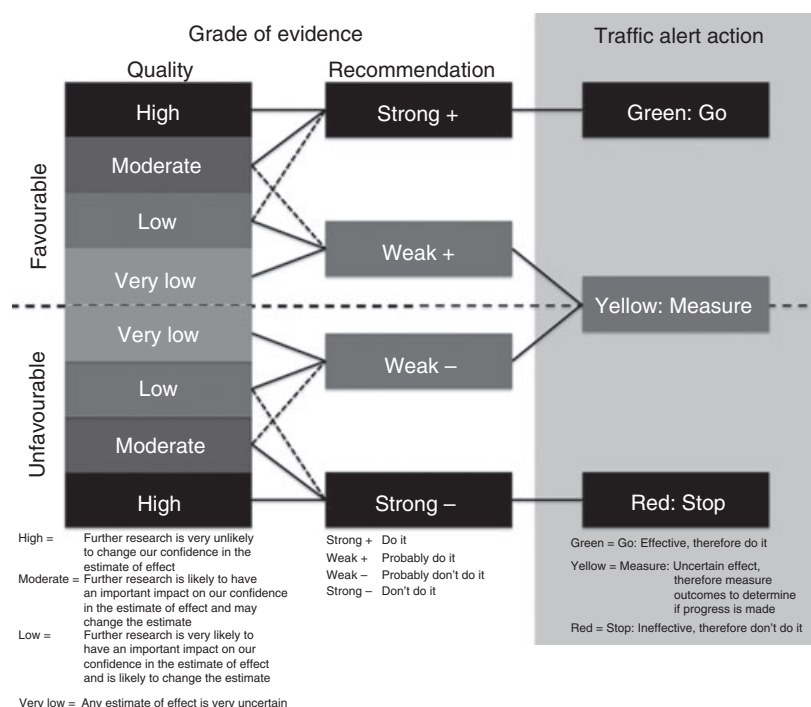
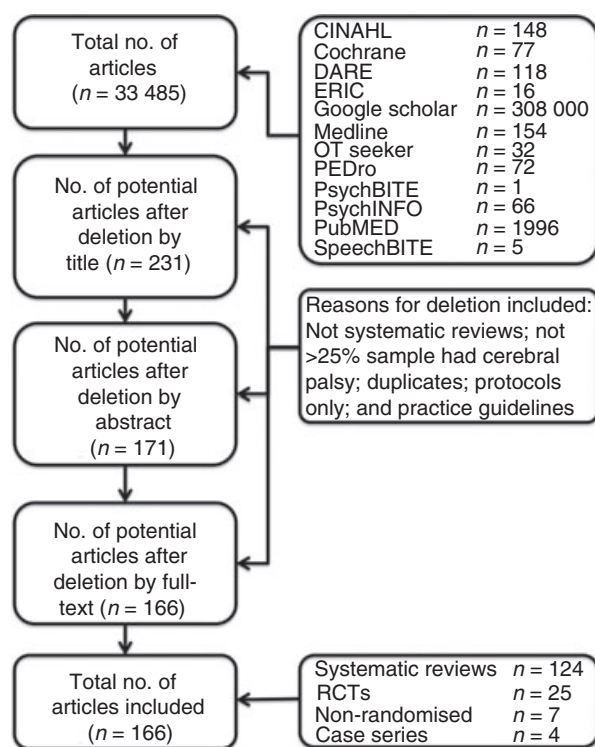Figure 1: Relationship between the GRADE and Traffic Light System.

Figure 2: Flow diagram of included articles.

166 included studies, the breakdown by level of evidence as rated on the Oxford Levels of Evidence was level 1 (*n*=124), 74%; level 2 (*n*=30), 18%; level 3 (*n*=6), 4%; and level 4 (*n*=6), 4%.

When the included articles were tallied in 5-year intervals by publication date, it was clear that the number of systematic reviews published about CP intervention had exponentially increased in recent years (Fig. 3).

Almost none (2 of 166) of the systematic reviews retrieved graded the body of evidence summarized using the GRADE system. We therefore carried out assignment of GRADEs using the recommended expert panel methodology. Using the GRADE system, of the 64 different CP interventions reviewed across 131 intervention outcomes 16% of outcomes assessed (*n*=21) were graded 'do it' (i.e. green light, go interventions); 58% (*n*=76) were graded 'probably do it' (i.e. yellow light, measure outcomes); 20% (*n*=26) were graded 'probably do not do it' (i.e. yellow light, measure outcomes; see Fig. 1); and 6% (*n*=8) were graded 'do not do it' (i.e. red light, stop interventions; see Fig. 1). In line with the appraisal criteria for this review, occupational therapy, physiotherapy, and medicine were the disciplines that encompassed the highest number of proven effective interventions for CP within their evidence base, which is not surprising given the long historical research emphasis on redressing the physical aspects of CP. In the fields of psychology, speech pathology, social work, and education, the evidence base for all interventions reviewed was lower level or inconclusive (yellow), but, in keeping with interdisciplinary care, psychologists and social
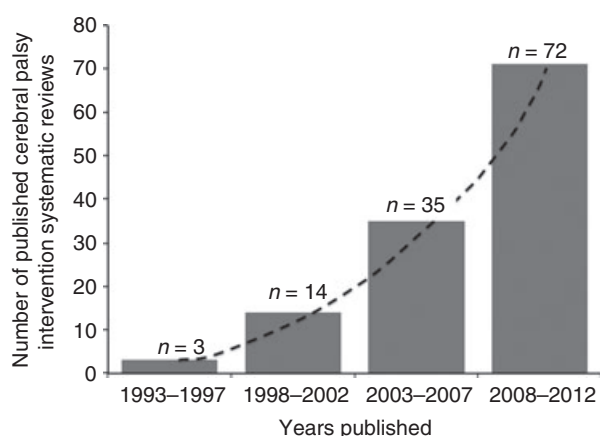
Figure 3: Number of published cerebral palsy intervention systematic reviews.

workers applied high-level evidence from other diagnostic groups (e.g. bimanual, cognitive behaviour therapy, counselling, Triple P[49]). In the field of speech pathology, it is worth noting that it is difficult to conduct studies of augmentative and alternative communication (AAC) using conventional rigorous methodologies because included participants often have different disability types and, accordingly, differing levels of expressive, receptive, and social communication abilities. AAC interventions require multifactorial measurement because effective device utilization relies on changes in all of these domains from best-practice speech, language, and teaching strategies and from changing the mode of communication. Thus, adequately measuring and attributing interventions effects to each component of these integrated treatment approaches remains challenging. Amongst the alternative and complementary medicine interventions offered by some clinicians, the findings were of even poorer quality, because an even greater proportion of the interventions were proven ineffective. However, the real rate of ineffective alternative and complementary interventions may be even higher as so many had to be excluded from this review as a result of the lack of any published peer-reviewed literature about the approaches (e.g. advanced biomechanical rehabilitation).

Each intervention was coded using the ICF by the intervention's desired outcome. Out of the 131 intervention outcomes for children with CP identified in this study, $n=66$ (51%) were aimed at the body structures and function level; $n=39$ (30%) were aimed at the activity level; $n=7$ (5%) were aimed at the participation level; $n=8$ (6%) were aimed at the environment level; and the remaining $n=11$ (8%) were aimed at combinations of ICF levels.

Green light go interventions
In the papers retrieved, the following CP interventions were shown to be effective: (1) botulinum toxin (BoNT), diazepam, and selective dorsal rhizotomy for reducing muscle spasticity; (2) casting for improving and maintain-ing ankle range of motion; (3) hip surveillance for maintaining hip joint integrity; (4) constraint-induced movement therapy, bimanual training, context-focused therapy, goal-directed/functional training, occupational therapy following BoNT, and home programmes for improving motor activity performance and/or self-care; (5) fitness training for improving fitness; (6) bisphosphonates for improving bone density; (7) pressure care for reducing the risk of pressure ulcers; and (8) anticonvulsants for managing seizures (despite no CP-specific anticonvulsant evidence existing, the panel rated the strength of the recommendation as strong plus (do it) because good-quality evidence supports anticonvulsants in non-CP populations,[191] and serious harm, even death, can arise from no treatment).

Green light effective interventions were mapped against the ICF by the outcomes that had been measured in the literature and the corresponding traffic light code was applied (Table II). First, Table II shows that green-light effective interventions were all aimed at either the body structures and function level or the activities levels on the ICF. The conspicuous finding here was that there were no proven effective interventions for addressing the participation, environment, or personal factors levels of the ICF, even though these are philosophical priorities. Second, Table II shows that when effective body structures and functions interventions were measured for an effect at the activities level (all of the time) evidence of effect was either lower level or inconclusive and, therefore, was coded yellow light. In other words, the positive effects of body structure interventions did not translate 'upstream' to the activities level. This finding seems to suggest that you 'get what you give'. This finding has, however, an alternative interpretation – we do not yet know if body structures and functions intervention improves outcomes at the activities level because of the measurement artefact created by randomized trials only being powered to detect change in one primary end-point. Third, Table II shows that green light activity-level interventions were effective at the activities level of the ICF, but minimal measurement had been undertaken to illuminate whether or not there was also any translation of impact 'downstream' to the body structures and functions level.

Yellow light measure outcomes interventions
A high proportion (70%) of the CP interventions within clinical care had either lower-level evidence supporting their effectiveness or inconclusive evidence, including acupuncture; alcohol (intramuscular injections for spasticity reduction); AAC; animal-assisted therapy; assistive technology; baclofen (oral); behaviour therapy and coaching; cognitive behaviour therapy; communication training; conductive education; counselling; oral dantrolene; dysphagia management; early intervention (for motor outcomes); electrical stimulation; fundoplication; gastrostomy; hand surgery; hip surgery; hippotherapy; hydrotherapy; intrathecal baclofen; massage; orthoses; oral–motor

Table II: Green light interventions (and their other indications) by level of ICF

Intervention	ICF level				
	Body structures and function	Activity	Participation	Environment	Personal factors
Body structures and function interventions					
1. Anticonvulsants	G				
2. Botulinum toxin	G				
3. Bisphosphonates	G				
4. Casting (ankle)	G	Y			
5. Diazepam	G				
6. Fitness training	G	Y	Y		
7. Hip surveillance	G				
8. Pressure care	G				
9. Selective dorsal rhizotomy	G	Y	Y		
Activities interventions					
10. Bimanual training		G			
11. Constraint-induced movement therapy		G			
12. Context-focused therapy		G			
13. Goal-directed training/functional training		G			
14. Home programmes		G	Y		
15. Occupational therapy post botulinum toxin (upper limb)		G			

G=green intervention when aimed at this level of the International Classification of Functioning, Disability and Health (ICF); Y=yellow intervention when aimed at this level of the ICF.

therapy; orthopaedic surgery; parent training; phenol (intramuscular injections); play therapy; respite; seating and positioning; sensory processing; single-event multilevel surgery; social stories; solution-focused brief therapy; strength training; stretching; therasuits; oral tizanidine; treadmill training; oral vitamin D; Vojta; and whole-body vibration. It is important to note that cognitive–behavioural therapy,[192–196] early intervention,[196–198] parent training,[49,50] and solution-focused brief therapy[199] all have good-quality supporting evidence in non-CP populations. It is also important to note that oral–motor therapy[200] and sensory processing[201] have equivocal evidence in non-CP populations for which they were designed, and so there is no strong or compelling reason to think either intervention would work better in CP. Of note, there was great variability in the volume and quality of the evidence available at the yellow-light level. For example, some intervention evidence bases were downgraded to low quality, as per the GRADE guidelines for dealing with imperfect randomized controlled trials (e.g. hippotherapy and biofeedback). However, for some interventions simply next to no evidence has been published and what has been published involves very small numbers and is of low quality (e.g. whole-body vibration).

The yellow-light included reviews that could not demonstrate robust evidence of effectiveness when strict systematic review criteria about design quality, adequate sample size, and independent replication were used to judge the evidence. Yellow-light reviews contained only marginal amounts of good-quality evidence when criteria were applied to reduce the possibility of biases explaining the proposed treatment benefits. Most yellow-light systematic review authors commented upon the low quality of the

designs used, serious methodological flaws, the relevance and sensitivity of the outcomes measures adopted, the difficulty in assembling large homogeneous samples for niche interventions, and most authors concluded that more rigorous research was needed.

Red light stop interventions

Craniosacral therapy, hip bracing, hyperbaric oxygen, NDT, and sensory integration have all been shown to be ineffective in children with CP, and are therefore not recommended for standard care. Appropriately, effective alternatives exist that seek to provide the same clinical outcome of interest.

To assist with comparative clinical decision-making amongst intervention options for the same desired outcome, we mapped the interventions that seek to provide analogous outcomes using bubble charts. In the bubble charts, the size of the circle correlated to the volume of published evidence. The circle size was calculated using (1) the number of published papers on the topic; and (2) the total score for the level of evidence (calculated by reverse coding of the Oxford Levels of Evidence, i.e. expert opinion=1, randomized controlled trial [RCT]=5). The location of the circle on the y-axis of the graph corresponds to the GRADE system rating. The colour of the circle correlates to the Evidence Alert System (Fig. 4).

DISCUSSION

High levels of evidence existed in the literature summarizing intervention options for children with CP. Akin to other fields of medicine and allied health, there has been an exponential increase in the number of systematic reviews published about CP intervention[6] revealing the emergence of

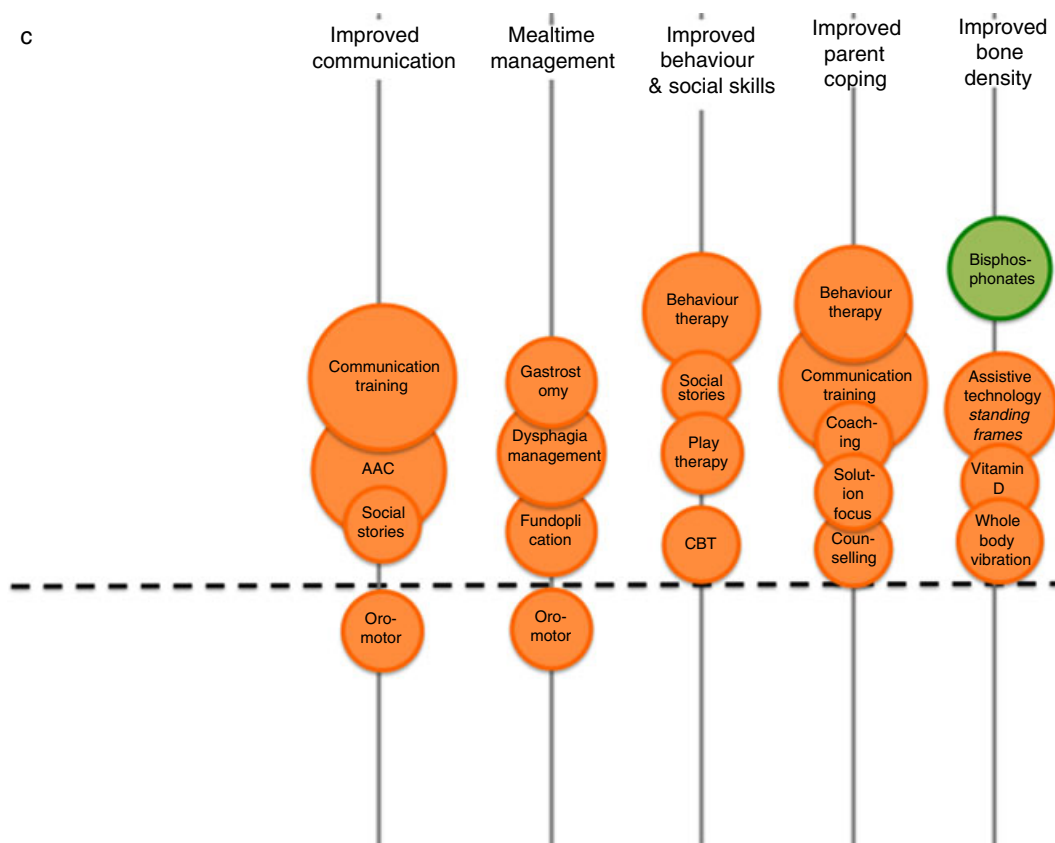**Figure 4:** State of the evidence for cerebral palsy intervention by outcomes.

Figure 4: Contiued.

highly effective prevention interventions.[186,187] There is no reason to think that this trend may decline. This finding has important implications for managers, knowledge brokers, and clinicians about finding effective and efficient ways for health professionals to remain up to date with the latest practice. Best available knowledge translation evidence suggests that managers and senior clinical mentors can help staff maintain up-to-date knowledge via interactive evidence-based practice continuing education sessions and journal clubs, but multiple tailored strategies will be required to change their use of evidence.[202] This systematic review could form the basis of policy, educational, and knowledge translation material because it is a comprehensive summary of the evidence base.

Recommendations for practice

Based upon the best available evidence, standard care for children with CP should include the following suite of interventions options (where the interventions would address the family's goals): (1) casting for improving ankle range of motion for weight bearing and/or walking; (2) hip surveillance for maintaining hip joint integrity; (3) bimanual training, constraint-induced movement therapy, context-focused therapy, goal-directed/functional training, and/or home programmes for improving motor activities

or self-care function; (4) BoNT, diazepam, or selective dorsal rhizotomy for spasticity management; (5) fitness training for aerobic fitness; (6) pressure care for reducing the risk of ulcers; (7) bisphosphonates for improving bone mineral density; and (8) anticonvulsants for managing seizures. When delivering interventions to children with CP, it is paramount that clinicians choose evidence-based interventions at the activities and participation level that hone the child's strengths and reflect their interests and motivations, and ultimately seek to help children live an inclusive and contented life. However, when choosing interventions at the body structure and functions level, the primary purpose is to mitigate the natural history of CP (such as hip dislocation) and the probable physical decline from secondary impairments,[118] rather than trying to fix the condition. We must also remain mindful that conflicts can arise between what families hope for and what the evidence suggests will be helpful or is realistically possible.[202] Part of being truly family centred is to act as an information resource to the family, which will include honest and open disclosure about prognosis using evidence-based tools to guide these difficult conversations.[203] Similarly, designing services based upon goals set by the family[5,64] is best practice and can also help to set the scene for discussing what is realistic and possible from intervention.

Going forward, systematic and disciplined use of outcome measures within all specialties is required for generating new evidence and confirming treatment effects of commonly used interventions. Routine outcome measurement is especially important when yellow-light interventions are being applied, and could circumnavigate some of the genuine research barriers including low availability of research funds and difficulties in assembling large homogenous samples. This recommendation is particularly vital for the fields of speech pathology, social work, and psychology that provide key services to children with CP, without strong evidence, as of yet, to support their practice. These professions have been overshadowed in the CP research arena until recently, when the field stopped solely redressing physical impairments and started to look further afield to engendering outcomes in well-being and participation. In addition, systematic and disciplined use of outcome measures is also needed when prescribing assistive technology and assistive devices (such as wheelchairs, walking frames, and communication devices) for children with CP, because devices form a large part of standard care. To date, specialized equipment and technology has been vastly under-researched, probably because the benefits are easily observable (such as independent mobility) and the studies are expensive to conduct; however, in light of device abandonment issues and associated costs, extensive efficacy research is warranted at both an individual and a population level. Moreover, prescribing assistive technology with a specialized appearance (such as orthotics, suits, computerized devices, robotics) may well elevate expectations of good outcomes and give rise to an overinflated perception of high-quality expert care. Thus, it is essential to know if the interventions are working, so as to prevent device abandonment, false hopes, and unnecessary effort.

When yellow-light interventions are used, it is imperative that clinicians utilize a sufficiently sensitive outcome measure to confirm whether or not the intervention is working and if it is helping the child achieve their family's goals. The Canadian Occupational Performance Measure (COPM) and Goal Attainment Scaling (GAS)[5,64,204] have been widely adopted in the literature for assessing goal achievement because they are valid, reliable, sensitive to change, and clinically affordable. Moreover, both measures work well within the family-centred approach because they encourage family-led goal setting and facilitate individualization, which is important for such a heterogeneous condition as CP. For yellow-light interventions, in addition to measuring whether goals are achieved, it may be desirable to measure if the intervention is actually achieving what it purports to do for each individual. Systematic individual outcome measurement, conducted at a population level with data aggregation, would introduce the possibility of rapidly expanding the evidence base amongst this heterogeneous population.

Parents, young people, and doctors have identified eight consensus measurement domains, important for assessing the impact of a CP intervention, that span the ICF levels.[205] We identified systematic reviews that provided measurement recommendations for evaluating these eight domains in a way that was sensitive to change. The first of these eight domains is impairment, which can be subdivided into (1) spasticity, measured using the Modified Tardieu Scale[5,64] and (2) fine motor, measured using the Melbourne Assessment of Unilateral Upper Limb Function[11] and the Quality of Upper Extremity Skills Test.[11] The second domain is general health. Valid and reliable instruments exist regarding general health in the literature, but less is understood about whether these measures are sensitive to change in CP, and therefore no recommendations are made at this juncture. Third is the gross motor skills domain, measured using the Gross Motor Function Measure.[73,206,207] The fourth domain is self-care/fine motor skills, which can be subdivided into (a) self-care, measured using the Paediatric Evaluation of Disability Inventory[206] and the Activities Scale for Kids[207,208] and (b) fine motor, measured using the Assisting Hand Assessment for activities performance measurement.[11] Fifth is the speech/communication domain, measured using GAS.[209] The sixth domain is integration/participation which can be measured using the COPM or GAS[204] (note that other domain-specific measures exist such as the LIFE-H, but this does not have adequate sensitivity to detect change). Finally, regarding both the seventh domain, quality of life, and the eighth domain, caregiver instruments, valid and reliable instruments exist in the literature, but less is understood about whether these measures are sensitive to change, and therefore recommendations for use are not made at this juncture.

In line with the principles of evidence-based care and as a cost-saving measure, it is highly recommended that craniosacral therapy, hip bracing, hyperbaric oxygen, neurodevelopmental therapy, and sensory integration should all be discontinued from CP care. Interestingly, these ineffective interventions for the most part are founded upon out-dated neurological theories about CP. For example, hyperbaric oxygen as a treatment for CP was based on the now disproven assumption that all CP arises from a lack of oxygen during birth (true for only 5–10% of cases[190]) and that increased oxygenation ought to help repair brain function. Neurodevelopmental therapy sought to reduce hyper-reflexia by repositioning the limb on stretch, providing a local pattern-breaking effect mimicking spasticity reduction, but we now know (1) that local effects do not translate to a reduction in centrally driven spasticity long term[210]; and (2) that no substantive evidence exists to support the idea that inhibition of primitive reflex patterns promotes motor development.[12] Likewise, 'bottom-up' approaches, in which children's underlying motor deficits are treated with the aim of preparing them for function (such as neurodevelopmental therapy and sensory integration) were commendable pursuits when originally invented but disappointingly have little carryover into functional activities.[12]

Over a decade ago, CP research experts[12] and systematic review authors called for 'concerted efforts to investigate other therapy approaches that may prove more clearly beneficial'.[142] These therapy experts were referring to

performance-based or 'top-down' approaches based on motor learning theory, in which interventions focus directly on specific task training in activities of interest and are not concerned with underlying impairments in body structures and function.[201] This visionary advice, in concert with the researchers who rigorously tested their theories, has transformed CP rehabilitation in recent years. The majority of the 'do it' or green-light effective CP therapy evidence generated in the last 10 years are in fact top-down therapy approaches, aimed at improving activities performance and inducing neuroplasticity, and include bimanual training, constraint-induced movement therapy, context-focused therapy, goal-directed/functional training, occupational therapy after toxin, and home programmes. Consistent with the theoretical underpinnings, research has not focused on whether these top-down approaches had a positive effect at the body structures and function level of the ICF (Table II).

Given the sudden increase in new effective treatment options available, it is essential that the field widely embraces and implements these interventions in order to ensure that children with CP achieve the best possible outcomes. Adoption of evidence-based practice also involves the difficult task of getting clinicians to stop providing ineffective treatments that they 'love'.[211] It has been suggested that the field requires professionals 'who want to do the best they can for their patients, who are willing to continually question their own managements, and who have readily available sources of information about what does work'.[211] Our present systematic review seeks to provide the CP field with a comprehensive overview about what works for children with CP and what does not (Fig. 4). Based on best available evidence, the challenge now is for the field to stop permissive endorsement of proven ineffective interventions on the basis of perceived low risk and clinical expertise. This recommendation includes ceasing provision of the ever-popular NDT. This is because NDT has been a mainstay physiotherapy and occupational therapy treatment for many years, but for the most part, the evidence base is unfavourable. Of note, contemporary NDT therapists eclectically include additional evidence-based treatment approaches under the NDT banner (e.g. motor learning and the philosophy of family-centred practice), and it is difficult to distil which treatment approaches are being used with fidelity and what features of the treatment are actually working.

Nevertheless, three systematic reviews have been conducted of traditional NDT,[141–143] including 18 discrete RCTs: 15 measuring efficacy and three measuring optimal dose. Of the 15 RCTs measuring NDT efficacy, 12 trials (studying 674 children) found no statistically favourable benefits from NDT; these trials were of varying quality (high, moderate, and low), whereas three trials (studying 38 children) showed improvements in body structures and functions such as gait parameters, spirometry, and milestone acquisition. The three favourable trials were all at high risk of bias when assessed using the Cochrane criteria,

including small sample sizes ($n<16$) and extremely low methodological quality such as a lack of blinding, intention-to-treat analysis, concealed allocation, etc. In the three NDT dosing RCTs, two studies (studying $n=96$ children) found no difference between intense or regular NDT, whereas one more recent study, by Tsorlakis[212] ($n=34$), showed favourable outcomes from higher-intensity NDT over lower-intensity NDT. The most recent NDT systematic review[143] cited the Tsorlakis[212] RCT as the sole high-level evidence for NDT being favourable, excluding older evidence and thus all the unfavourable NDT RCTs. Since this is not a standard systematic review methodology for providing proof of efficacy, the results of this systematic review[143] should be interpreted with caution. The difference in inclusion criteria between the systematic reviews explains why the newer systematic review[143] suggests a more favourable benefit from NDT than the earlier systematic reviews that concluded ineffectiveness.[141,142]

In order to determine the strength of recommendation, the panel weighed up the balance of benefits and harms from NDT and concluded that there was strong evidence that NDT does not improve contracture and tone, along with weak evidence that NDT does not improve function. This was because, first, when the methodological quality of the evidence base was considered, the highest quality evidence suggested NDT was ineffective, with only low-quality, high risk of bias studies finding a favourable benefit from NDT. Second, the importance of the outcome that NDT aims to prevent was considered: (1) regarding contracture, which is painful and can limit function, high-quality RCTs showed that casting was a superior treatment to NDT for contracture management and therefore the panel favoured casting; (2) regarding tone reduction, the highest quality evidence suggested that NDT was ineffective for this indication and other evidence shows BoNT exists as a highly effective alternative and therefore the panel favoured BoNT or other effective pharmacological agents. Third, the magnitude and precision of treatment effect was considered: only 3 out of 15 trials found any benefit of NDT, and in these studies the treatment effects were small with very low precision estimates as a result of methodological flaws. Fourth, the burdens and costs of the therapy were considered: NDT is time-consuming and expensive for families, and, what is more, a high-quality RCT shows that substantially better functional motor gains are achieved from motor learning than from NDT at equal doses.[213] Therefore, despite the evidence being less well understood for the likelihood of NDT influencing functional motor gains (yellow light), the panel favoured motor learning since superior gains were possible from an equal dose. Furthermore, since no other body structure and function intervention in this review showed gains beyond the body structure and function level up into the activity level, it is hard to imagine why NDT would be the exception to this trend.

In summary, high-quality evidence demonstrates that casting is superior to NDT for managing contracture; BoNT exists as a highly effective alternative to NDT for

managing tone since NDT is ineffective for this indication; and despite less being known about whether NDT improves function, high-quality evidence indicates that motor leaning is superior to NDT for improving function. Consequently, there are no circumstances where any of the aims of NDT could not be achieved by a more effective treatment. Thus, on the grounds of wanting to do the best for children with CP, it is hard to rationalize a continued place for traditional NDT within clinical care.

Recommendations for research

In future, systematic review authors should assign a GRADE to the body of evidence summarized, to enable clinicians to more quickly interpret the findings of the review for clinical practice. For the motor learning interventions that were 'green light', researchers have repeatedly called for future investigations to determine optimal dosing, to better assess the widely held belief that 'more is better'. Understanding optimal intensity of therapy is important for maximizing outcomes, accurately costing services, and offering family-friendly, achievable interventions. For all the green-light interventions, additional studies that evaluate long-term outcomes are necessary. First, because families of children with CP have life-long caregiving responsibilities, an understanding the impact of these time-intensive and expensive interventions would help with expectation management and planning for lifetime care. Second, it is unknown if some interventions continue to add an incremental benefit when used repeatedly over years or whether the gains are one-off and short term only. Long-term outcome data are essential for costing and optimizing the outcomes of children with CP.

For the yellow-light interventions with lower-quality evidence or a paucity of research to support effectiveness, recommendations for research include the use of individual patient meta-analyses to accelerate data aggregation; collaborations that strategize multicentre data collection to overcome sample size barriers; and the use of CP registries and single-system designs if RCTs are deemed impossible or ethically undesirable to conduct. Use of these research methodologies is advisable and appropriate across all disciplines but would have particular value if applied to the disciplines of orthopaedic surgery, speech pathology,[214–216] and social work, in order to better substantiate the important contributions these clinicians make to CP care. The CP field would also benefit from social workers and psychologists confirming the assumed benefits of proven interventions from non-CP populations amongst children with CP.

When the whole evidence base was viewed from a global perspective, there was a startling lack of interventions available to improve children's participation within their community. Given that this has been identified by many of the systematic review authors as a priority area for intervention, more research designed to measure the effects of participation interventions and funds dedicated to this end is urgently needed. Furthermore, until participation-specific measures with sensitivity to change have been developed, researchers need to measure the effects of participation intervention using GAS or the COPM.

Study limitations

All systematic reviews are prone to publication bias from the included trial data; therefore, this systematic review of systematic reviews may incorporate this inherent bias. There is also no guarantee that absolutely all relevant systematic reviews were retrieved, despite the thorough search strategy. Publication bias, however, is unlikely to be more of a problem when identifying systematic reviews than when identifying clinical trials. Moreover, conducting a systematic review of systematic reviews is a study limitation in its own right because the method does not create any information that was not already available. Furthermore, using a high-level synthesis helicopter view means that specific intervention details about how the intervention took place, who benefitted from the intervention, and for how long the intervention was carried out for were not reported; clinicians would need to turn to the included papers to obtain this information. In its place we hope that the knowledge synthesis will help to bridge the gap between research and practice by providing comparisons of varying interventions to aid decision making.

CONCLUSION

In conclusion, we found compelling evidence from systematic reviews to suggest that the following interventions are effective at the body structures and function level alone: anticonvulsants, ankle casting, BoNT, bisphosphonates, diazepam, fitness training, hip surveillance, pressure care, and selective dorsal rhizotomy. We also found compelling evidence from systematic reviews to suggest that the following interventions improve function at the activities level: bimanual training, constraint-induced movement therapy, context-focused therapy, goal-directed/functional training, home programmes, and occupational therapy after BoNT. No interventions were shown to work conclusively at more than one level of the ICF. Therefore, if a body structures and function outcome is desired, the intervention must be selected from the suite of evidence-based body structures and function interventions. Conversely, if an activities-level outcome is sought, top-down learning interventions, acting at the activities level, must be applied.

The lack of certain efficacy evidence for large proportions of the interventions in use within standard care is a problem for people with CP, healthcare providers, purchasers of healthcare, and funders. More research using rigorous designs is urgently needed as CP is the most common physical disability of childhood with a life-long impact.[190]

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table SI: Search strategy.

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