Pharmacological and neurosurgical interventions for individuals with cerebral palsy and dystonia: a systematic review update and meta-analysis

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ABBREVIATIONS

BADS	Barry Albright Dystonia Scale
BFMDRS	Burke–Fahn–Marsden Dystonia Rating Scale
DBS	Deep brain stimulation
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
ITB	Intrathecal baclofen
MCID	Minimal clinically important difference
QoL	Quality of life
RCT	Randomized controlled trial
SMD	Standardized mean difference

AIM To update a systematic review of evidence published up to December 2015 for pharmacological/neurosurgical interventions among individuals with cerebral palsy (CP) and dystonia.

METHOD Searches were updated (January 2016 to May 2020) for oral baclofen, trihexyphenidyl, benzodiazepines, clonidine, gabapentin, levodopa, botulinum neurotoxin (BoNT), intrathecal baclofen (ITB), and deep brain stimulation (DBS), and from database inception for medical cannabis. Eligible studies included at least five individuals with CP and dystonia and reported on dystonia, goal achievement, motor function, pain/comfort, ease of caregiving, quality of life (QoL), or adverse events. Evidence certainty was evaluated using GRADE.

RESULTS Nineteen new studies met inclusion criteria (two trihexyphenidyl, one clonidine, two BoNT, nine ITB, six DBS), giving a total of 46 studies (four randomized, 42 non-randomized) comprising 915 participants when combined with those from the original systematic review. Very low certainty evidence supported improved dystonia (clonidine, ITB, DBS) and goal achievement (clonidine, BoNT, ITB, DBS). Low to very low certainty evidence supported improved motor function (DBS), pain/comfort (clonidine, BoNT, ITB, DBS), ease of caregiving (clonidine, BoNT, ITB), and QoL (ITB, DBS). Trihexyphenidyl, clonidine, BoNT, ITB, and DBS may increase adverse events. No studies were identified for benzodiazepines, gabapentin, oral baclofen, and medical cannabis.

INTERPRETATION Evidence evaluating the use of pharmacological and neurosurgical management options for individuals with CP and dystonia is limited to between low and very low certainty.

Dystonia is a movement disorder characterized by 'sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both'.[1] It is frequently present in individuals with cerebral palsy (CP)[2,3] and can impact function, pain/comfort, ease of caregiving, and quality of life (QoL).[4–7] While dystonia management often involves pharmacological, neurosurgical intervention, or both, a systematic review including studies published up to December 2015 found limited evidence to support their use among individuals with CP and dystonia, leading to a care pathway based predominantly on clinical expert opinion.[8,9] Given the limited evidence supporting these management options and consequent variability in prescribing practices,[5] there is a need to conduct an up to date review of the evidence to include newly published studies and use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach[10] to optimize quality and clarity. GRADE is highly suited to situations where evidence is limited, as it encourages synthesis of best-available evidence (direct and indirect), whether it can be quantitatively pooled or used to develop a narrative summary.[11]

This systematic review addresses this need by updating the original version published by Fehlings et al. in 2018.[8] It is not, however, a mechanistic repetition, but rather has been conducted to reflect current standards in systematic review methodology with the use of GRADE and to incorporate an additional intervention (medical cannabis) and outcomes (achievement of individualized goals, QoL) important to clinicians and individuals with CP and their families. Quantitative meta-analyses, where possible, have allowed comparisons between pooled estimates and

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thresholds for clinical meaningful change, avoiding limitations associated with vote-counting approaches based on statistical thresholds. Finally, the GRADE approach has guided a rigorous evidence appraisal process and enhanced the clarity of findings by informing statements that communicate the direction and certainty of effects demonstrated across included studies.[12]

The specific question addressed by this review is the following: in individuals with CP and dystonia, what is the effect of receiving a pharmacological or neurosurgical intervention (oral baclofen, benzodiazepines, clonidine, gabapentin, levodopa, trihexyphenidyl, botulinum neurotoxin [BoNT], intrathecal baclofen [ITB], deep brain stimulation [DBS], or medical cannabis), compared with not receiving the intervention, receiving a placebo, or an alternative intervention, on dystonia, achievement of individualized goals, motor function, pain/comfort, ease of caregiving, QoL, and adverse events? As recommended by the GRADE Working Group,[13] this review acts as the first step in preparing for guideline development by providing an objective and comprehensive synthesis of best-available direct evidence. Importantly, this first step of the systematic review also helps to define where indirect evidence will be required. The second step will use the systematic review, along with additional evidence from indirect populations where required, to develop a forthcoming clinical practice guideline and updated care pathway.

What this paper adds

- Meta-analysis suggests that intrathecal baclofen (ITB) and deep brain stimulation (DBS) may improve dystonia and pain.
- Meta-analysis suggests that DBS may improve motor function.
- Clonidine, botulinum neurotoxin, ITB, and DBS may improve achievement of individualized goals.
- ITB and DBS may improve quality of life.
- No direct evidence is available for oral baclofen, benzodiazepines, gabapentin, or medical cannabis.

METHOD

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[14] A protocol was prospectively registered with PROSPERO (CRD42020152969).

Literature search

Search strategies were aligned with those from the original review and used Medical Subject Headings and keyword variations for the interventions (oral baclofen, benzodiazepines, clonidine, gabapentin, levodopa, trihexyphenidyl, BoNT, ITB, DBS, medical cannabis) and population of interest.[8] To minimize the impact of varied nomenclature, terms targeting dyskinetic CP were also incorporated.

Searches were conducted from the end of the original search period (January 2016) to May 2020 for interventions included in the original review, and from database inception to May 2020 for medical cannabis. The databases searched included Ovid MEDLINE, CINAHL, AMED, Cochrane Reviews, Embase, and EBM Reviews, in addition to clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform. Reference lists were also examined for eligible studies. The strategy used in MEDLINE and adapted for other databases is provided in Table S1 (online supporting information).

Study selection

The inclusion criteria were the following: (1) English-language full-text studies; (2) at least one outcome of interest (dystonia, achievement of individualized goals, motor function, pain/comfort, ease of caregiving, QoL, adverse events); (3) at least five participants with CP and dystonia receiving an intervention of interest (oral baclofen, benzodiazepines, clonidine, gabapentin, levodopa, trihexyphenidyl, BoNT, ITB, DBS, or medical cannabis); and (4) at least 50% of participants with CP and dystonia (either alone, as a component of dyskinetic CP, or presenting in combination with spasticity and/or choreoathetosis). Studies were also included if fewer than 50% of participants had CP and dystonia, so long as the sub-sample included at least five participants with CP and dystonia and results were reported separately. Studies reporting on individuals with dyskinetic CP, but confirmed to present with dystonia through author correspondence, were also eligible. Given the limited availability of randomized controlled trials (RCTs),[8] and to provide a comprehensive overview of best available evidence, both randomized (i.e. RCTs, crossover trials) and non-randomized studies (i.e. cohort studies, uncontrolled case series with before–after measurements, uncontrolled retrospective surveys/reviews of medical records) were eligible regardless of the outcome measures used. Measures informing each outcome are detailed in Table S2 (online supporting information). Studies were included irrespective of the comparator (i.e. either not receiving the intervention of interest, receiving a placebo, or receiving an alternative intervention). No restrictions were placed on timeframe or setting.

Records were managed using a Web-based program (DistillerSR, Evidence Partners, Ottawa, Canada). After duplicate removal, titles and abstracts were screened independently by two reviewers and reasons for exclusion were recorded. Studies deemed potentially eligible were reviewed in full-text by two reviewers. Discrepancies were resolved through discussion and, if required, consultation with a third reviewer.

Data extraction

Data from new studies and those included in the original review[8] were extracted by two independent reviewers using a custom form documenting study characteristics (author, year, title, country, study design, trial size, follow-up, funding sources), participant characteristics (diagnosis, covariates, age, sex), intervention details (description, dose, duration, frequency), and results (outcome measures, results, statistical tests). If results were reported by subsample, only data from individuals with CP and dystonia were extracted and used to inform the analysis. Any

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discrepancies were resolved through discussion and, if required, consultation with a third reviewer.

Risk of bias assessment

The Cochrane Collaboration Risk of Bias 2.0 tool was used to evaluate risk of bias in randomized studies, with domains addressing bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.[15] As the non-randomized body of evidence comprised exclusively uncontrolled case series with before–after measurements and retrospective surveys/reviews of medical records, a custom tool (Appendix S1, online supporting information) was developed to address the issues most pertinent to these study designs, as emphasized by the Cochrane Handbook for Systematic Reviews of Interventions.[12] The domains addressed by this tool are aligned with those of the ROBINS-I:[16] development and application of appropriate eligibility criteria, intervention and outcome measurement, confounding, incomplete/inadequate follow-up, and selective reporting. Risk of bias was assessed independently by two reviewers at the outcome level. Discrepancies were resolved through discussion and, if required, consultation with a third reviewer. For outcomes with at least 10 studies, funnel plots were generated. Asymmetry was assessed by visual inspection and using Begg's rank correlation test to help evaluate whether publication bias was 'undetected' or 'strongly suspected'.[17] In the case of significant results, adjusted effect sizes were calculated using the trim-and-fill method.

Data synthesis

A random effects meta-analysis was performed if studies were sufficiently homogenous and the majority reported findings in a way that allowed an effect size calculation. Forest plots were generated using Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) and RStudio (RStudio Team, Boston, MA, USA). In cases where I^2 ≥50%, reasons for heterogeneity were explored when evaluating inconsistency.[12] Where meta-analysis was not feasible, findings were summarized narratively following synthesis without meta-analysis principles[18] and differences in the direction and magnitude of effects across studies were considered.[11]

Effect sizes were estimated using data recorded at baseline and last follow-up for studies with pre-/post-comparisons, and as the difference in means between intervention and comparator for within-participant measures for crossover trials. If all studies for a continuous outcome reported on the same measure, a mean difference (MD) and 95% confidence interval (CI) were calculated. If different instruments were used, a standardized mean difference (SMD) and 95% CI were calculated. In cases where some scales increased with severity while others decreased, effect sizes were multiplied by −1 to ensure that a change in the same direction indicated an improvement. For dichotomous outcomes, the relative risk (RR) and corresponding anticipated absolute effects were calculated. For ordinal scales, the responses were dichotomized into 'improvement' (i.e. any extent of improvement reported by the individual scale) or 'no improvement' (i.e. no change or worsening). Results from pooled analyses were compared with established minimal clinically important differences (MCIDs), if available. Information required to inform meta-analyses was sought through author correspondence where necessary. If participant-level findings were available, only data from individuals with CP and dystonia with both pre- and post-intervention measures were included. Data were reviewed for duplicate participants, where possible, and participants included in multiple studies (as determined by identical sex, age in years, and Burke–Fahn–Marsden Dystonia Rating Scale [BFMDRS]-Movement]) were retained only in the study with the longest follow-up.

Rating evidence certainty

The GRADE framework[10] was used to evaluate evidence certainty across new studies and those identified in the original review. GRADE assigns one of four levels of evidence certainty (high, moderate, low, very low) for each outcome across studies. Evidence from randomized and non-randomized studies start at high and low certainty respectively. This initial rating is increased or decreased according to eight factors: study limitations (risk of bias), inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose–response relationship, and plausible confounding.[10] Dystonia and achievement of individualized goals were designated as critical for decision-making, while motor function, pain/comfort, ease of caregiving, and QoL were considered important, but not critical for decision-making. Adverse events were designated as critical for ITB and DBS, and important for pharmacological interventions. Randomized and non-randomized bodies of evidence were appraised separately, and the body of evidence of higher certainty informed conclusions. Evidence profiles were developed using GRADEpro GDT (GRADEPro Guideline Development Tool, McMaster University, Hamilton, Ontario, Canada).

RESULTS

A total of 1493 records were retrieved. After removal of duplicates, the titles and abstracts of 826 unique records were screened, of which 682 were excluded (Fig. S1, online supporting information). After full-text screening, 19 new studies satisfied all criteria (two trihexyphenidyl, one clonidine, two BoNT, nine ITB, six DBS), for a total of 46 studies when combined with those from the original review.[8] Of the included studies, there were four randomized trials, 34 uncontrolled case series with before–after measurements, and eight retrospective studies with no comparison (e.g. surveys, chart reviews). Studies excluded at this stage are documented in Appendix S2 (online supporting information). One study included in the original systematic review was deemed ineligible upon further

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review and was excluded from this update.[19] No articles evaluating oral baclofen, benzodiazepines, gabapentin, or medical cannabis were identified.

An overview of characteristics of the included studies is provided in Table S3 (online supporting information), with more detailed information available in Appendix S3 (online supporting information). A summary of the directions of effect and certainty of evidence for each intervention and outcome is provided in Table 1. The GRADE evidence profiles in Appendix S4 (online supporting information) provide a summary of the magnitude, direction, and certainty of evidence for each intervention and outcome.

Oral baclofen

No studies evaluating oral baclofen were identified.

Trihexyphenidyl

The evidence for trihexyphenidyl comprises one randomized crossover trial[20] and six non-randomized studies,[21–26] two of which were identified in the updated search (Appendix S3). The certainty of both bodies of evidence was very low for all outcomes (Appendix S4). The randomized body of evidence (one study; *n*=16) suggested little to no effect on dystonia, achievement of individualized goals, or motor function, with changes in the Barry Albright Dystonia Scale (BADS; MD 0.9; 95% CI −2.2 to 3.9), Goal Attainment Scale (MD 6.8; 95% CI −3.7 to 17.5), Canadian Occupational Performance Measure (performance: MD 0.8; 95% CI −0.5 to 2.0; satisfaction: mean difference 0.7; 95% CI −0.3 to 1.8), and Quality of Upper Extremity Skills Test (MD −1.6; 95% CI −6.3 to 3.1) failing to meet suggested MCIDs.[27,28] While variability in outcome reporting in the body of non-randomized evidence precluded pooling, individual studies demonstrated little to no important change in dystonia (five studies; *n*=207), motor function (five studies; *n*=224), ease of caregiving (two studies; *n*=124), and QoL (one study; *n*=23). No studies reported on pain/comfort. Trihexyphenidyl may result in little to no difference in dystonia, achievement of individualized goals, motor function, ease of caregiving, and QoL, compared with not receiving trihexyphenidyl, in individuals with CP and dystonia (GRADE very low certainty).

The body of randomized evidence (one study; *n*=16) suggested an increased risk of adverse events with trihexyphenidyl (RR 2.5; 95% CI 1.4–4.7), with events including agitation, constipation, dry mouth, and poor sleep.[20] This finding is supported by the body of non-randomized evidence (four studies; *n*=177), which reported 23% to 69% of participants to experience adverse events.[21–23,25] Trihexyphenidyl may increase the risk of adverse events, compared with not receiving trihexyphenidyl, in individuals with CP and dystonia (GRADE very low certainty).

Benzodiazepines

No studies evaluating benzodiazepines were identified.

Clonidine

The body of evidence for clonidine comprises a single uncontrolled retrospective case series identified in this update, which evaluated individuals with severe dystonia

Table 1: Summary of evidence certainty ratings and directions of effect

		Direction of effect (by outcome) GRADE evidence certainty (by outcome)						
Intervention	Studies (*n*)	Dystonia	Goal achievement	Motor function	Pain/comfort	Ease of caregiving	Quality of life	Adverse events
Oral baclofen	0	–	–	–	–	–	–	–
Trihexyphenidyl	7	Little to no difference ⊕OOO	Little to no difference ⊕OOO	Little to no difference ⊕OOO	–	Little to no difference ⊕OOO	Little to no difference ⊕OOO	May increase ⊕OOO
Benzodiazepines	0	–	–	–	–	–	–	–
Clonidine	1	May improve ⊕OOO	May improve ⊕OOO	–	May improve ⊕OOO	May improve ⊕OOO	–	May increase ⊕OOO
Gabapentin	0	–	–	–	–	–	–	–
Levodopa	1	–	–	Little to no difference ⊕OOO	–	–	–	Little to no difference ⊕OOO
Medical cannabis	0	–	–	–	–	–	–	–
Botulinum neurotoxin	5	Little to no difference ⊕⊕OO	May improve ⊕OOO	Little to no difference ⊕⊕OO	May improve ⊕⊕OO	May improve ⊕OOO	Little to no difference ⊕OOO	May increase ⊕⊕OO
Intrathecal baclofen	14	May improve ⊕OOO	May improve ⊕OOO	Little to no difference ⊕⊕OO	May improve ⊕OOO	May improve ⊕OOO	May improve ⊕OOO	May increase ⊕OOO
Deep brain stimulation	19	May improve ⊕OOO	May improve ⊕OOO	May improve ⊕OOO	May improve ⊕OOO	–	May improve ⊕OOO	May increase ⊕OOO

Certainty of evidence ratings: high, ⊕⊕⊕⊕; moderate, ⊕⊕⊕O; low, ⊕⊕OO; very low, ⊕OOO. GRADE, Grading of Recommendations, Assessment, Development and Evaluations.

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(*n*=24 [14 of whom had CP]; Appendix S3).[29] Evidence certainty was assessed as very low for all outcomes, and findings are limited by the lack of blinding, absence of pre-intervention measurements, and subjective nature of outcome reporting (Appendix S4). Carers' reports suggested improvements in dystonia, achievement of individualized goals, sleep, and seating in most participants. Clonidine may improve dystonia, achievement of individualized goals, pain/comfort, and ease of caregiving, compared with not receiving clonidine, among individuals with CP and dystonia (GRADE very low certainty).

The included study also reported side effects in 50% of participants, with events including drowsiness (*n*=9), increased movements (*n*=3), and decreased sleep (*n*=1), leading to discontinuation in five participants.[29] Clonidine may increase the risk of adverse events, compared with not receiving clonidine, among individuals with CP and dystonia (GRADE very low certainty).

Gabapentin

No studies evaluating gabapentin were identified.

Levodopa

No new studies for levodopa were identified and the evidence continues to comprise a single randomized crossover trial (*n*=9; Appendix S3).[30] Evidence certainty was assessed as very low for all outcomes (Appendix S4). While results were not available for dystonia, pain/comfort, ease of caregiving, or QoL, there was no difference in Quality of Upper Extremity Skills Test scores (measuring motor function) when comparing measures following the last dose of levodopa with placebo (MD −2.3; 95% CI −34.6 to 29.9).[30] Levodopa may result in little to no difference in motor function, compared with not receiving levodopa, in individuals with CP and dystonia (GRADE very low certainty).

No adverse events were reported after levodopa or placebo; however, side effects were not systematically evaluated. Levodopa may result in little to no difference in the risk of adverse events, compared with not receiving levodopa in individuals with CP and dystonia (GRADE very low certainty).

Medical cannabis

No studies evaluating medical cannabis were identified.

BoNT

One randomized crossover trial[31] and four non-randomized studies[32–35] evaluating BoNT were identified, with the RCT[31] and one non-randomized study[35] representing new additions (Appendix S3). The certainty of the randomized and non-randomized bodies of evidence was assessed as low and very low respectively (Appendix S4). The low certainty body of randomized evidence (one study; *n*=16) demonstrated little to no difference in dystonia and motor function, with the Toronto Western Spasmodic Torticollis Rating Scale scores falling below established MCIDs (Toronto Western Spasmodic Torticollis Rating Scale severity MD −2.1; 95% CI −7.6 to 3.5; Toronto Western Spasmodic Torticollis Rating Scale disability MD 0.06; 95% CI −3.2 to 3.3). Very low certainty non-randomized evidence suggested possible improvements in dystonia (one study; *n*=7) and upper extremity motor function (two studies; *n*=29), although these findings are attributed to studies at high risk of bias in which approaches to outcome reporting (*p*-values reported only) prohibited interpretation in the context of MCIDs.[33,35] While the randomized body of evidence (one study; *n*=16) reported a reduction in pain just shy of the two-point MCID (Toronto Western Spasmodic Torticollis Rating Scale pain MD −1.7; 95% CI −3.9 to 0.57), a clinically meaningful improvement was observed between baseline and after BoNT (mean difference −2.6; 95% CI −5.2 to 0.0) and not baseline and saline (mean difference 1.7; 95% CI −0.4 to 3.8).[31,36] The very low certainty body of non-randomized evidence also supported pain reduction (one study; *n*=26).[34] BoNT may result in little to no difference in dystonia and motor function, but may reduce pain, compared with not receiving BoNT in individuals with CP and dystonia (GRADE low certainty).

The very low certainty body of non-randomized evidence supported improvements in both achievement of individualized goals (two studies; *n*=36)[32,34] and ease of caregiving (one study; *n*=22),[35] but no change in QoL (one study; *n*=7).[33] These findings are limited to subjective carers' impressions, preventing meaningful interpretation of the magnitude of effects. BoNT may improve achievement of individualized goals and ease of caregiving, but result in little to no difference in QoL, compared with not receiving BoNT, in individuals with CP and dystonia (GRADE very low certainty).

Adverse events were reported by four studies. The body of randomized evidence (one study; *n*=16) suggested an increased risk of dysphagia after BoNT among individuals with cervical dystonia (RR 2.0; 95% CI 0.20–19.9).[31] Very low certainty evidence from the non-randomized body of evidence (two studies; *n*=15) reported transitory weakness (focal to treated limb or unspecified location) to occur in up to 40% of participants.[32,33] BoNT may result in an increased risk of adverse events, compared with not receiving BoNT in individuals with CP and dystonia (GRADE low certainty).

ITB

One RCT[28] with 3-month follow-up and 13 non-randomized studies[37–49] evaluating ITB were identified (Appendix S3). The RCT and seven non-randomized studies represent new additions. The certainty of both bodies of evidence was very low (Appendix S4). The randomized evidence (one study; *n*=33) reported little to no difference in dystonia (BADS MD −1.3; 95% CI −4.8 to 2.2; Dyskinesia Impairment Scale dystonia subscale MD −8.0%; 95% CI −16.9 to 0.94).[28] Conversely, the body of non-randomized evidence (five studies; *n*=69) suggested an

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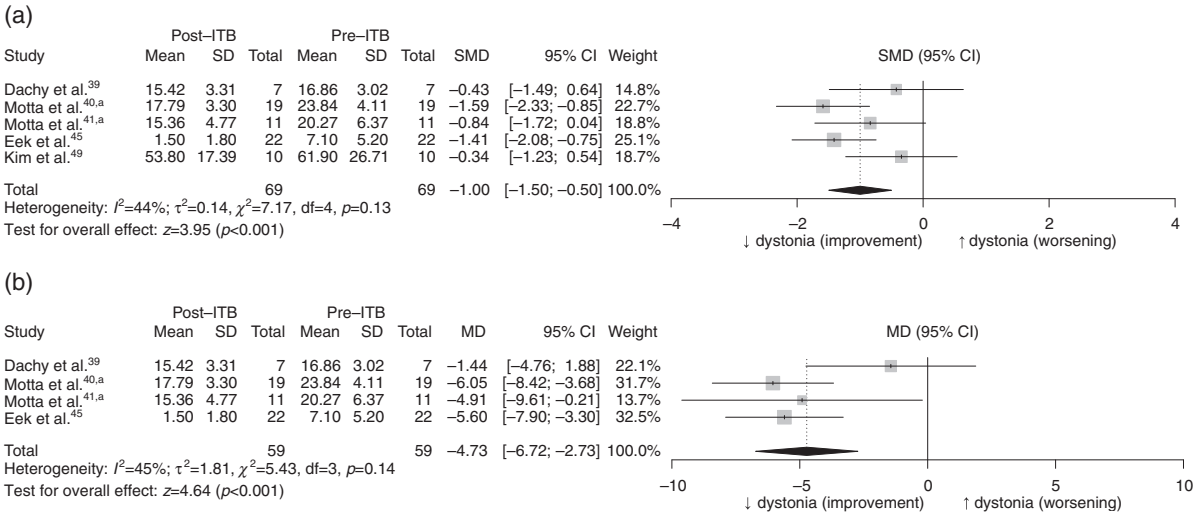

Figure 1: Forest plot of random effects meta-analysis of non-randomized studies for dystonia before and after intrathecal baclofen (ITB). (a) Standardized mean difference (SMD) across all studies reporting on dystonia (Barry Albright Dystonia Scale [BADS] or Burke–Fahn–Marsden Dystonia Rating Scale – Movement). (b) Mean difference (MD) across studies reporting on BADS only. [a]There is potential for participant overlap between Motta et al.[40] and Motta et al.[41] although sufficiently detailed participant-level data were not provided to confirm the extent of duplicate participants. SD, standard deviation; CI, confidence interval.

improvement (SMD −1.0; 95% CI −1.5 to −0.50; MD [BADS only] −4.7; 95% CI −6.7 to −2.7; Fig. 1).[39–41,45,49] The weighted percentage improvement across studies reporting on the BADS exceeded the suggested MCID of 25% (43.1%; 95% CI 11.4–74.8).[28] The difference in findings between the randomized and non-randomized bodies of evidence may be a result of the RCT's 3-month follow-up period, which might have been insufficient to reach optimal dosing. ITB may improve dystonia, compared with not receiving ITB, in individuals with CP and dystonia (GRADE very low certainty).

The randomized body of evidence suggested improved motor function (one study; *n*=36), as reported by the proportion of mobility-related goals at least partly achieved (RR 9.3; 95% CI 1.4–63).[28] The non-randomized body of evidence (four studies; *n*=37) suggested no change in motor function across studies reporting on a validated outcome measure (SMD 0.13; 95% CI −0.33 to 0.59; Fig. 2).[41,45,46,49] The varying effects observed between the two bodies of evidence may be due to differences in outcomes measures used (i.e. goal- vs function-oriented). ITB may result in little to no difference in motor function, compared with not receiving ITB in individuals with CP and dystonia (GRADE very low certainty).

The body of randomized evidence (one study; *n*=36) supported improved pain/comfort, as assessed by achievement of goals related to pain, comfort, or sleep (RR 4.8; 95% CI 0.8–30).[28] This improvement is supported by the body of non-randomized evidence (two studies; *n*=28) reporting on validated scales (SMD 0.87; 95% CI 0.30–1.4; Fig. 3). Both non-randomized studies exceeded the MCIDs for their respective measures.[48,49] ITB may reduce pain, compared with not receiving ITB, in individuals with CP and dystonia (GRADE very low certainty).

Both randomized and non-randomized evidence supported improvements in achievement of individualized

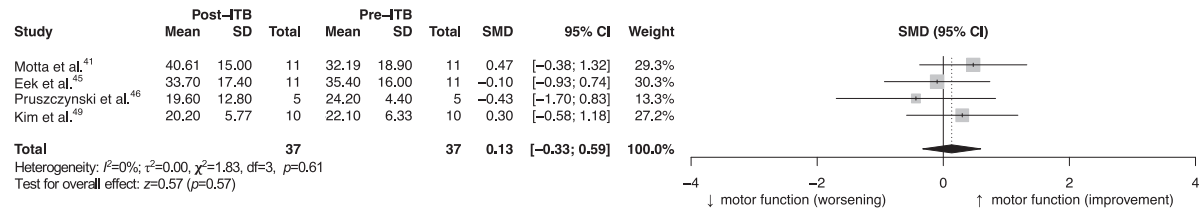

Figure 2: Forest plot of random effects meta-analysis of non-randomized studies reporting on motor function (Burke–Fahn–Marsden Dystonia Rating Scale – Disability, Gross Motor Function Measure, or Melbourne Assessment of Unilateral Upper Limb Function) before and after intrathecal baclofen (ITB). SD, standard deviation; CI, confidence interval; SMD, standardized mean difference.

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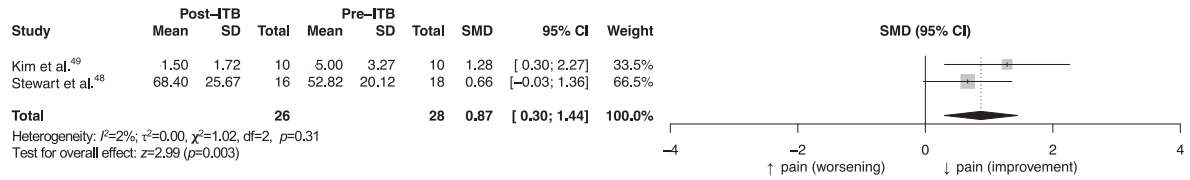

Figure 3: Forest plot of random effects meta-analysis of non-randomized studies reporting on pain (visual analogue scale or the Caregivers Priorities and Child Health Index of Life with Disabilities Questionnaire [comfort and emotions]) before and after intrathecal baclofen (ITB). SD, standard deviation; CI, confidence interval; SMD, standardized mean difference.

goals and ease of caregiving. The body of randomized evidence (one study; *n*=33) reported participants receiving ITB to achieve considerably higher Goal Attainment Scale T scores (MD 17.9; 95% CI 11.2–24.6) and attain a higher proportion of goals specific to caregiving (RR 29; 95% CI 1.9–455).[28] The non-randomized body of evidence included one study (*n*=25) reporting 76% of participants to have fully reached their predefined goals,[45] and one study (*n*=18) reporting an improvement just shy of the MCID reported in the self-care domain of the Caregiver Priorities and Child Health Index of Life with Disabilities questionnaire (MD 9.4; 95% CI 1.2–17.6).[48] The non-randomized body of evidence (one study; *n*=18) also supported an improvement in QoL (Caregiver Priorities and Child Health Index of Life with Disabilities mean difference 9.2; 95% CI 0.23–18.1). ITB may improve achievement of individualized goals, ease of caregiving, and QoL, compared with not receiving ITB in individuals with CP and dystonia (GRADE very low certainty).

The body of randomized evidence (one study; *n*=36) demonstrated no difference in the number of participants who experienced at least one adverse event (RR 1.0; 95% CI 0.26–3.8).[28] Several events were attributed to surgery/pump implantation (e.g. liquor leakage, infection), which both groups underwent. Data pertaining to adverse events were also reported by eight non-randomized studies (*n*=199).[37,38,40,41,43,45,47,49] Overall adverse event rates in the non-randomized body of evidence were between 26% and 78%,[38,43] and common complications included cerebrospinal fluid leakage (8–74%), infection (4–39%), and catheter problems (5–21%). ITB may result in an increased risk of adverse events, compared with not receiving ITB, in individuals with CP and dystonia (GRADE very low certainty).

DBS

Nineteen non-randomized studies[49–67] evaluating DBS were identified, including six new studies (Appendix S3). Evidence certainty was assessed as very low for all outcomes (Appendix S4). A meta-analysis across 16 studies (*n*=173) suggested an improvement in dystonia (SMD −0.60; 95% CI −0.89 to −0.31; Fig. 4a).[49–51,53,54,56–62,64–67] Follow-up was between 6 months and 4 years 5 months. A similar improvement was demonstrated when considering studies reporting on the most common timepoint of 12 months (SMD −0.64; 95% CI −1.0 to −0.25). The MD across 15 studies (*n*=168) reporting on the BFMDRS-Movement was −12.1 (95% CI −18.1 to −6.1), equating to a weighted percentage improvement of 16.8% (95% CI 8.7–25.0), just meeting an MCID of 16.6% established among individuals with primary dystonia (Fig. 4b).[68] While the funnel plot suggested possible publication bias for the analysis of all studies, asymmetry was not detected for the analysis of studies reporting on the BFMDRS-Movement (Fig. S2, online supporting information). DBS may improve dystonia, compared with not receiving DBS in individuals with CP and dystonia (GRADE very low certainty).

Eleven studies (*n*=109) reporting on motor function informed the meta-analysis, which demonstrated an improvement (SMD −0.30; 95% CI −0.57 to −0.04; Fig. 5a).[49–51,53–57,62,64,66] The change across only studies reporting on the BFMDRS-Disability surpassed the MCID of 0.5 points established among individuals with primary dystonia (MD −1.1; 95% CI −2.4 to 0.22; Fig. 5b).[68] This finding is limited by serious risk of bias and imprecision. Publication bias was undetected (Fig. S2). DBS may improve motor function, compared with not receiving DBS in individuals with CP and dystonia (GRADE very low certainty).

Five studies (*n*=78) reported on validated measures of pain/comfort and informed a meta-analysis demonstrating an improvement in pain/comfort (SMD 1.0; 95% CI 0.28–1.7; Fig. 6a).[49,50,52,64,67] When considering only trials reporting on the 36-item Short-Form Health Survey (four studies; *n*=50), an improvement exceeding the suggested MCID of 5.1 points was observed (MD 26.8; 95% CI 10.9–42.6; Fig. 6b).[68] This finding is limited by serious study limitations, imprecision, and inconsistency as a result of heterogeneity in the magnitude of effect across studies. DBS may improve pain, compared with not receiving DBS in individuals with CP and dystonia (GRADE very low certainty).

Improvements in achievement of individualized goals and QoL were supported by the non-randomized body of evidence. Clinically significant changes in Canadian Occupational Performance Measure performance and satisfaction scores were evident in 54% to 100% and 54% to

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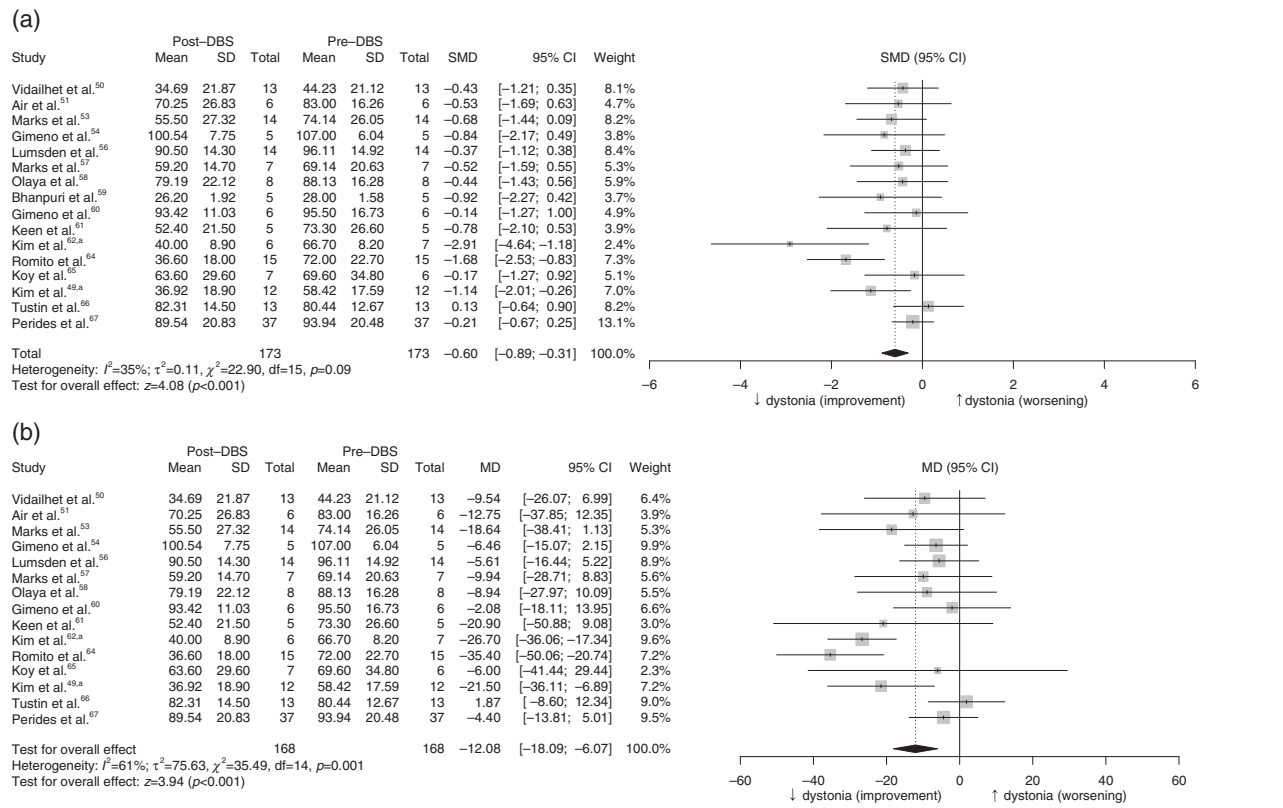

Figure 4: Forest plot of random effects meta-analysis of non-randomized studies reporting on dystonia before and after deep brain stimulation (DBS). (a) Standardized mean difference (SMD) across all studies reporting on dystonia (Burke–Fahn–Marsden Dystonia Rating Scale – Movement [BFMDRS-M] or Barry Albright Dystonia Scale). (b) Mean difference (MD) across studies reporting on BFMDRS-M only. [a]There is potential for participant overlap between Kim et al.[62] and Kim et al.[49] although sufficiently detailed participant-level data were not available confirm the extent of duplicate participants. SD, standard deviation; CI, confidence interval.

80% of participants at 12 months respectively (two studies; n=18).[54,60] A single study (n=5) reported on the Goal Attainment Scale, with participants achieving an average of 67% of their goals at 12 months.[54] Four studies (n=50) reported on the 36-item Short-Form Health Survey, and physical functioning, vitality, and mental health domains were used to estimate the effect on QoL. Improvements surpassing MCIDs established among individuals with primary dystonia[68] were demonstrated in all three domains (physical functioning: MD 11.4 [95% CI −4.6 to 27.4]; vitality: MD 13.4 [95% CI 5.3–21.6]; mental health: MD 12.9 [95% CI 4.6–21.1]).[49,50,52,64] DBS may improve achievement of individualized goals and QoL, compared with not receiving DBS, in individuals with CP and dystonia (GRADE very low certainty).

Twelve non-randomized studies (n=117) reported on adverse events, with overall rates ranging from 0% to 40%.[49–54,57–59,61,63,64] The most common events included infections requiring hardware removal (7–40%)[51,53,57,61,64] and stimulation-induced dysarthria (17–30%).[49,52,64] DBS may result in an increased risk of adverse events, compared with not receiving DBS in individuals with CP and dystonia (GRADE very low certainty).

DISCUSSION

Understanding the evidence related to pharmacological and neurosurgical interventions for individuals with CP and dystonia is important, given the prevalence of dystonia among individuals with CP and its impact on function, pain, caregiving, and QoL.[2,4–7] This systematic review synthesizes this body of evidence, which includes 46 total studies (four randomized, 34 uncontrolled case series with before–after measurements, and eight retrospective studies with no comparison). The use of GRADE has guided rigorous evidence appraisal and, for ITB and DBS, meta-analyses have allowed us to interpret findings in the context of MCIDs. This update includes studies published over an additional 3-year period, one new intervention (medical cannabis), and three additional outcomes (achievement of individualized goals, QoL, adverse events). Key differences between the original review and this update are attributed to the inclusion of new publications and implementation of the GRADE framework.

Pharmacological management

While oral medications are used for individuals with CP and dystonia, evidence for their effectiveness and safety is

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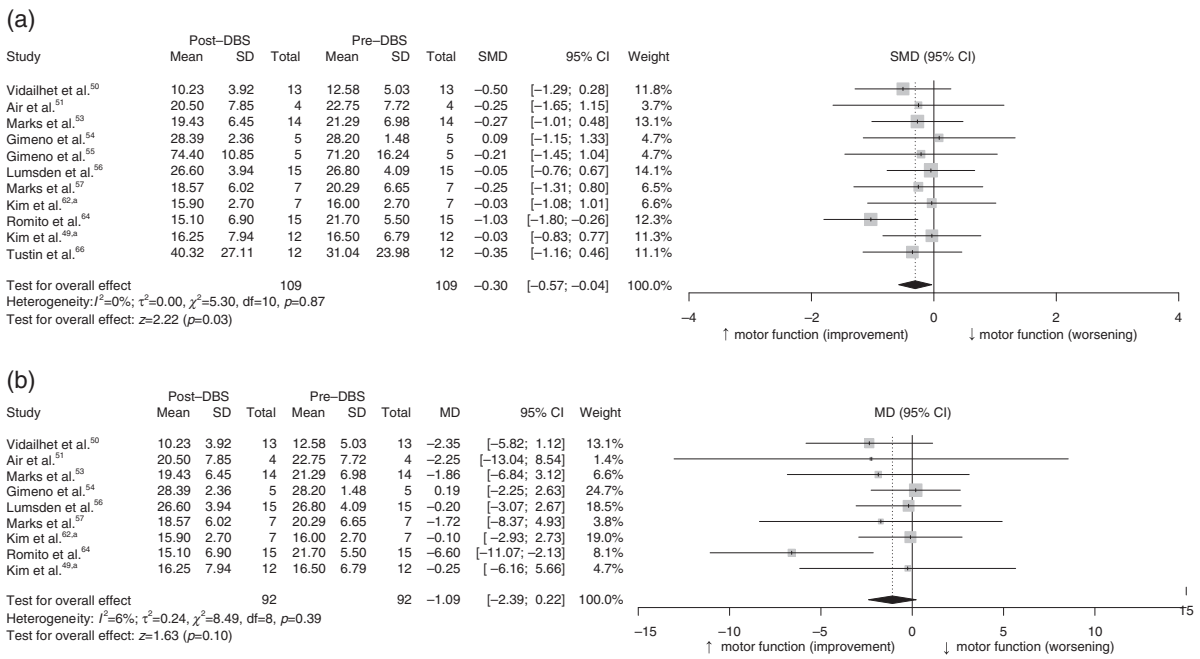

Figure 5: Forest plot of random effects meta-analysis of non-randomized studies reporting on motor function before and after deep brain stimulation (DBS). (a) Standardized mean difference (SMD) across all studies reporting on motor function (Burke–Fahn–Marsden Dystonia Rating Scale – Disability [BFMDRS-D], Gross Motor Function Measure 88, Melbourne Assessment of Unilateral Upper Limb Function). (b) Mean difference (MD) across studies reporting on BFMDRS-D only. [a]There is potential for participant overlap between Kim et al.[62] and Kim et al.[49] although sufficiently detailed participant-level data were not available confirm the extent of duplicate participants. SD, standard deviation; CI, confidence interval.

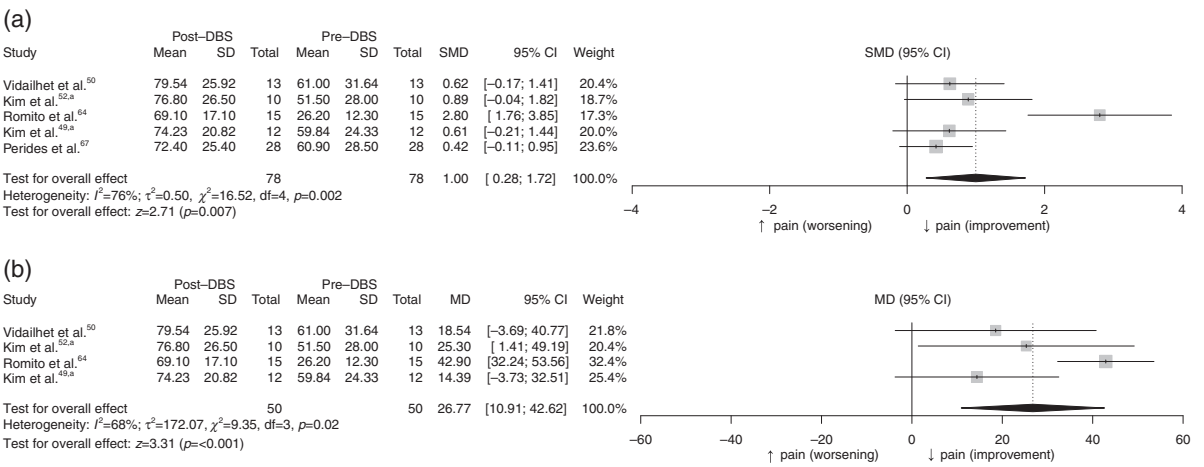

Figure 6: Forest plot of random effects meta-analysis of non-randomized studies reporting on pain before and after deep brain stimulation (DBS). (a) Standardized mean difference (SMD) across all studies reporting on pain (36-item Short-Form Health Survey [SF-36] [bodily pain] or Caregivers Priorities and Child Health Index of Life with Disabilities Questionnaire [comfort and emotions]). (b) Mean difference (MD) across studies reporting on SF-36 only. [a]There is potential for participant overlap between Kim et al.[52] and Kim et al.[49] although sufficiently detailed participant-level data were not available confirm the extent of duplicate participants. SD, standard deviation; CI, confidence interval.

limited. Despite identifying three new publications (two trihexyphenidyl, one clonidine), our findings that trihexyphenidyl may result in little to no difference in dystonia, motor function, achievement of individualized goals, and ease of caregiving (GRADE very low certainty) are largely aligned with the 'possibly ineffective' designations from the original review. Trihexyphenidyl may increase the risk of adverse events (GRADE very low certainty), with cited events including agitation, constipation, dry mouth, and poor sleep. New evidence for clonidine suggested

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improvements in dystonia, achievement of individualized goals, pain, and ease of caregiving (GRADE very low certainty). Clonidine may also be associated with a risk of adverse events, including drowsiness and increased movements (GRADE very low certainty). These findings support a potential role of clonidine, although evidence is limited to one retrospective study reporting on subjective carer-reported impressions of change and including participants with and without CP (Appendix S4). Given these limitations, studies focusing specifically on individuals with CP and using standardized assessments are needed to decisively establish the place and potential benefit of clonidine in this context.

There continues to be a paucity of evidence for levodopa, oral baclofen, benzodiazepines, gabapentin, and medical cannabis among individuals with CP and dystonia. This is consistent with a systematic review of oral pharmacological management options for dyskinetic CP, which identified limited evidence with contradictory results.[69] Our finding that levodopa may result in little to no difference in motor function and risk of adverse events (GRADE very low certainty) is largely aligned with the original review's conclusion that levodopa is 'possibly ineffective' in improving motor function. No studies evaluating gabapentin, oral baclofen, benzodiazepines, or medical cannabis among individuals with CP and dystonia were identified. Studies specific to these management options in this population and using validated outcome measures are needed. This systematic review has therefore highlighted that indirect evidence will be required for oral baclofen, benzodiazepines, gabapentin and medical cannabis when completing the second step of the GRADE process where clinical practice recommendations are formulated.

The updated search identified a new randomized crossover trial, suggesting that BoNT may result in little to no difference in dystonia and motor function, but may reduce pain (GRADE low certainty).[31] This trial notably included participants older than 20 years (mean age 46y) with dyskinetic CP and cervical dystonia, while non-randomized evidence focused on pediatric populations (GRADE very low certainty). This crossover trial provides valuable new information, as the original review provided 'inadequate' data to assign levels of evidence for dystonia, motor function, and pain/comfort. We have also addressed an evidence gap for ease of caregiving with a single non-randomized study reporting most caregivers to report a positive effect on 'care burden', although this study is limited in its retrospective design and use of a non-validated outcome measure.[35] Very low certainty evidence also suggested improved achievement of individualized goals, but no important differences in QoL. It is important to note that concomitant reductions in spasticity may have contributed to improvements in pain and achievement of individualized goals reported, as some participants presented with mixed dystonia and spasticity. Finally, BoNT may increase the risk of adverse events (GRADE low certainty), including transient weakness and cervical dysphagia in individuals with cervical dystonia. Given some conflicting findings between randomized and non-randomized bodies of evidence and limited evidence evaluating ease of caregiving, achievement of individualized goals, and QoL, studies implementing validated outcome measures are needed to more precisely establish the impact of BoNT.

Neurosurgical management

To our knowledge, the included RCT is the first of its kind to evaluate ITB among individuals with CP and dystonia.[28] While changes in dystonia did not reach clinical significance, important differences in achievement of goals related to pain/comfort, ease of caregiving, and motor function were reported. However, this study is limited by the short follow-up period, which may have been insufficient to attain optimal dosing and response, contributing to a very low certainty designation. Given this limitation, it is helpful to consider the non-randomized body of evidence which, although also of very low certainty, reports on longer follow-up. Non-randomized evidence supported a clinically important improvement in dystonia, aligning with the 'possibly effective' designation in the original review. Our confidence in this estimate is limited by the small number of studies and wide CIs. Further, some change in dystonia may be attributable to concurrent improvements in spasticity, as some studies reported on individuals with mixed tone. Of the studies contributing to the meta-analysis, the most modest individual effect was attributed to a study in which participants received a single bolus injection,[39] which may suggest that bolus injections are less successful in reducing dystonia than continuous infusion through an implantable pump. The non-randomized body of evidence also suggested little to no change in motor function, but improvements in pain, ease of caregiving, achievement of individualized goals, and QoL. Common adverse events reported by the non-randomized evidence included cerebrospinal fluid leakage, pump or catheter infection, and catheter-related problems (including breaks and revisions), which can lead to withdrawal. Few catheter-related problems were documented by the RCT, although this is probably due to the short period of follow-up. The RCT reported the same number of participants in both groups to have experienced adverse events. Possible adverse drug effects (e.g. nausea and vomiting) were, however, more common among those receiving baclofen. As the effect of ITB is somewhat unclear owing to the inconsistency in findings between the non-randomized and randomized bodies of evidence, well-designed trials with concurrent controls and a period of follow-up of at least 12 months are needed.

The 19 included studies evaluating DBS comprised a body of non-randomized evidence of very low certainty for all outcomes. The limited evidence is consistent with recent reviews and meta-analyses of DBS for individuals with pediatric dystonia and dyskinetic CP.[70–72] The evidence suggests that DBS may improve dystonia, aligning

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with the original review's 'possibly effective' classification. Although data were previously inadequate to comment on motor function and pain/comfort, we found that DBS may improve these outcomes. Our confidence in the effect on motor function is especially limited owing to high risk of bias among included studies and a CI that slightly crosses the line of no treatment effect. The change in evidence rating for motor function is probably attributable to the use of alternative synthesis methods, given that only three new studies contributed to the analysis. For pain/comfort, this change can be attributed to the inclusion of new studies, as well as studies considered to be of insufficient quality (i.e. 'class IV') in the original review. The evidence also supported possible improvements in achievement of individualized goals and QoL. We found that DBS may increase the risk of adverse events, consistent with evidence from a large-scale prospective audit of surgery-related complications in children with dystonia of unspecified origin who underwent DBS.[73] Overall, more evidence is needed to support the use of DBS among individuals with CP and dystonia, with a particular emphasis on standardized measurement of individualized goals and thorough documentation of complications.

One may be inclined to compare SMDs for dystonia between baseline and 12 months after ITB (SMD −1.1; 95% CI −1.6 to −0.6) and DBS (SMD −0.64; 95% CI −1.0 to −0.25), and suggest that ITB is superior in reducing dystonia. However, we caution against direct comparison, given that these estimates were informed by different outcome measures. To enable comparison with established MCIDs, weighted percentage improvements were also computed. While the percentage improvement after ITB exceeded the suggested BADS MCID of 25% (43.1%; 95% CI 11.4–74.8%), this value just reached the BFMDRS-Movement MCID (16.6%) for DBS (16.8%; 95% CI 8.7–25.0%). While this interpretation might suggest that the magnitude of the effect on dystonia is greater with ITB, it is important to recognize that this estimate is limited by the small number of available long-term non-randomized studies compared with a greater number of studies for DBS. Ultimately, our ability to clinically interpret differences in the effect of ITB and DBS on dystonia depends on the conduct of future controlled studies directly comparing these interventions.

Limitations

A key limitation of this report is that the body of evidence is between low and very low certainty, limiting our ability to draw strong conclusions. Most of the evidence base comprises non-randomized studies of pre-/post-design, which are at high risk of bias. While RCTs were available to inform some outcomes for trihexyphenidyl, levodopa, BoNT, and ITB, these studies were also rated down to between low and very low certainty due to study limitations and imprecision. The variability in outcome measures used across studies also impeded direct comparison and limited meaningful interpretation in some cases. While pooled effect estimates were calculated to provide an impression of the magnitude of effect where possible, a quantitative analysis was not always feasible. It is also important to acknowledge that effect sizes may be biased and represent an overestimation of the true effect when applied to within-group non-randomized studies. Our interpretations are also limited by the paucity of available information related to MCIDs, which have not been formally established for several outcome measures reported among included studies, or have been established in populations other than dystonia in CP. Formal establishment of MCIDs specifically among individuals with CP and dystonia will allow a more accurate interpretation of the effects observed. Finally, it is possible that relevant studies may have been excluded if they were not published in the English language.

CONCLUSION

Evidence evaluating the use of pharmacological and neurosurgical management options for individuals with CP and dystonia is limited to between low and very low certainty. Levodopa may result in little to no difference in motor function and risk of adverse events. Trihexyphenidyl may have little to no effect on dystonia, goal achievement, motor function, ease of caregiving, and QoL. Clonidine may improve dystonia, goal achievement, pain/comfort, and ease of caregiving. While BoNT may improve goal achievement, pain/comfort, and ease of caregiving, it may have little to no effect on dystonia, motor function, and QoL. ITB may improve dystonia, goal achievement, pain/comfort, ease of caregiving, and QoL, but have little to no effect on motor function. DBS may result in improvements in dystonia, goal achievement, motor function, pain/comfort, and QoL. The risk of adverse events may increase with trihexyphenidyl, clonidine, BoNT, ITB, and DBS. No evidence was available for oral baclofen, benzodiazepines, gabapentin, or medical cannabis. Findings need to be interpreted with caution, given that evidence is of low to very low certainty according to GRADE. Studies with larger sample sizes, more rigorous study designs, and implementing validated outcome measures are required to better inform our understanding of the effectiveness and safety of pharmacological and neurosurgical interventions for dystonia in CP. Researchers are encouraged to include achievement of individualized goals (e.g. Canadian Occupational Performance Measure, Goal Attainment Scale) and QoL as outcomes in future studies. Given the heterogeneity of this population and challenges in recruiting sufficient numbers to conduct an RCT, other methodologies (e.g. N-of-1 trials, single case design with replications across centers) could be useful in generating more robust evidence. The findings of this systematic review will be interpreted by a multidisciplinary panel to inform the development of clinical recommendations forming the basis of an updated clinical practice guideline and care pathway (https://www.aacpdm.org/publications/care-pathways/dystonia).

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: PRISMA flow diagram.

Figure S2: Funnel plots assessing publication bias for DBS.

Table S1: Search strategy.

Table S2: Outcomes used for evidence evaluation.

Table S3: Characteristics of included studies.

Appendix S1: Risk of bias assessment: non-randomized studies.

Appendix S2: References excluded after full-text review.

Appendix S3: Characteristics and results reported by included studies.

Appendix S4: GRADE evidence profiles.

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INTERVENCIONES FARMACOLÓGICAS Y NEUROQUIRÚRGICAS PARA INDIVIDUOS CON PARÁLISIS CEREBRAL Y DISTONÍA: UNA ACTUALIZACIÓN DE REVISIÓN SISTEMÁTICA Y META- ANÁLISIS

OBJETIVO

Actualizar una revisión sistemática sobre evidencia publicada hasta Diciembre del 2015 para intervenciones farmacológicas y neuroquirúrgicas entre individuos con parálisis cerebral (PC) y distonía.

MÉTODO

Se actualizaron las búsquedas (desde Enero 2016 hasta Mayo del 2020) para baclofeno oral, trihexifenidilo, benzodiacepinas, clonidina, gabapentina, levodopa, neurotoxina botulinica (BoNT), baclofeno intratecal (ITB), y estimulación cerebral profunda (DBS), y desde el inicio de la base de datos para el cannabis medicinal. Los estudios elegibles incluyeron al menos 5 individuos con PC y distonía e informaron sobre distonía, logro de metas, función motora, dolor/comorbilidad, facilidad para brindar cuidados, calidad de vida (QoL) o eventos adversos. La certeza de la evidencia se evaluó mediante GRADE.

RESULTADOS

Diez y nueve estudios reunieron los criterios de inclusión (2 trihexifenidilo, uno clonidina, 2 BoNT, 9 ITB, 6 DBS). Cuando se combinan con los de la revisión sistemática original, dan un total de 46 estudios (cuatro aleatorios, 42 no aleatorios) que comprenden 915 participantes. Evidencia de certeza muy baja apoyó la mejoría de la distonía (clonidina, BoNT, ITB, DBS). La certeza baja a una muy baja apoyó una mejor función motora (DBS), dolor/comorbilidad (clonidina, BoNT, ITB, DBS), facilidad de cuidado (clonidina, BoNT, ITB) y CdV (ITB, DBS). Trihexifenidilo, clonidina, BoNT, ITB y DBS pueden aumentar los eventos adversos. No se identificaron estudios para benzodiacepinas, gabapentina, baclofeno oral, y cannabis medicinal.

INTERPRETACIÓN

La evidencia que evalúa el uso de opciones de manejo farmacológico y neuroquirúrgico para personas con parálisis cerebral y distonía se limita a evidencia entre baja y muy baja certeza.

INTERVENÇÕES FARMACOLÓGICAS E NEUROCIRÚRGICAS PARA INDIVÍDUOS COM PARALISIA CEREBRAL E DYSTONIA: UMA ATUALIZAÇÃO DE REVISÃO SISTEMÁTICA E METANÁLISE

OBJETIVO

Atualizar uma revisão sistemática da evidência publicada até dezembro de 2015 para intervenções farmacológicas/neurocirúrgicas entre indivíduos com paralisia cerebral (PC) e distonia.

MÉTODO

As buscas foram atualizadas (Janeiro 2016 a Maio 2020) quanto a baclofeno oral, triexifenidil, benzodiazepínicos, clonidina, gabapentina, levodopa, neurotoxina botulínica (NTBo), baclofeno intratecal (BIT), e estimulação cerebral profunda (ECB), e desde o início da base de dados para cannabis medicinal. Estudos elegíveis incluíram ao menos cinco indivíduos com PC e dystonia, e reportaram os objetivos atingidos, função motora, dor/conforto, facilidade do cuidado, qualidade de vida (QV), ou efeitos adversos. A certeza da evidência foi avaliada usando GRADE.

RESULTADOS

Dezenove novos estudos atenderam aos critérios de inclusão (dois com triexifenidil 1 com clonidina, dois com NTBo, nove com BIT e seis com ECB), dando um total de 46 estudos (quatro randomizados, 42 não randomizados) compreendendo 915 participantes quando combinados com aqueles da revisão sistemática original. Evidência com certeza muito baixa suporta a melhora da distonia (clonidina, BIT, ECB) e atingimento de objetivos (clonidina, NTBo, BIT, ECB). Evidência com certeza baixa a muito baixa apóia melhora da função motora (ECB), dor/conforto (clonidina, NTBo, BIT, ECB), facilidade de cuidado (clonidina, NTBo, BIT), e QV (BIT, ECB). Triexifenidil, clonidina, NTBo, BIT, e ECB podem aumentar efeitos adversos. Não foram identificados estudos com benzodiazepínicos, gabapentina, baclofeno oral, e cannabis medicinal.

INTERPRETAÇÃO

A evidência avaliando o uso de opções de manejo farmacológico e cirúrgico para indivíduos com PC e distonia é limitada a certeza baixa e muito baixa.

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