Pharmacological and neurosurgical interventions for managing dystonia in cerebral palsy: a systematic review

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ABBREVIATIONS

DBS	Deep brain stimulation
GABA	γ-Aminobutyric acid
ITB	Intrathecal baclofen

AIM To systematically review evidence for pharmacological/neurosurgical interventions for managing dystonia in individuals with cerebral palsy (CP) to inform a care pathway.
METHOD Searches included studies with a minimum of five participants with dystonia in CP receiving oral baclofen, benzodiazepines (clonazepam, diazepam, lorazepam), clonidine, gabapentin, levodopa, trihexyphenidyl, botulinum toxin, intrathecal baclofen (ITB), or deep brain stimulation (DBS). Evidence was classified according to American Academy of Neurology guidelines.
RESULTS Twenty-eight articles underwent data extraction: one levodopa, five trihexyphenidyl, three botulinum toxin, six ITB, and 13 DBS studies. No articles for oral baclofen, benzodiazepines, clonidine, or gabapentin met the inclusion criteria. Evidence for reducing dystonia was level C (possibly effective) for ITB and DBS; level C (possibly ineffective) for trihexyphenidyl; and level U (inadequate data) for botulinum toxin.
INTERPRETATION For dystonia reduction, ITB and DBS are possibly effective, whereas trihexyphenidyl was possibly ineffective. There is insufficient evidence to support oral medications or botulinum toxin to reduce dystonia. There is insufficient evidence for pharmacological and neurosurgical interventions to improve motor function, decrease pain, and ease caregiving. The majority of the pharmacological and neurosurgical management of dystonia in CP is based on clinical expert opinion.

Dystonia is 'a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both'.[1–4] Dyskinetic cerebral palsy (CP) is considered a common cause of dystonia in children and comprises 4% to 17% of all cases of CP, of which most are predominantly dystonic and others choreoathetotic.[5,6] Dystonia is increasingly recognized as coexisting with spastic subtypes of CP, where it is referred to as 'mixed' tone.[7] Nevertheless, dystonia in childhood CP remains underdiagnosed.[8,9] Dystonia may be associated with basal ganglia and cortical/subcortical lesions typically arising late in gestation or around birth.[10]

On neurological examination of individuals with CP, dystonia is characterized by the presence of fluctuating hypertonia and/or involuntary postures and movements triggered by arousal, such as wakening from sleep, tiredness, and lack of sleep; cognitive tasks; emotional state; and physiological phenomena, such as hunger and temperature, tactile stimulation, or voluntary movement.[7,8] The postures often have a twisting element such as equinovarus posturing of the foot. Dystonia can be generalized (numerous regions throughout the body are involved), focal (a single limb or truncal part is affected), or segmental (a few body regions are affected).[11] Dystonic movements and muscle contractions often decrease during sleep and fluctuate in severity over time.[2,3,11] Occasionally, a dystonic storm can occur, including status dystonicus, in which dystonic symptoms rapidly intensify to extreme, forceful, and repeated contractions.[12]

The presence of dystonia can impact motor function, pain/comfort, and ease of care for individuals with CP. Dystonia can impede motor function by involuntary muscle contractions, limitations in muscle relaxation, and overflow, which is the association of involuntary movement with intended movement that spreads to surrounding or distant muscles.[2] The twisting movements and abnormal

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postures that characterize dystonia can be painful,[8,11,13,14] with dystonia identified as the second most common cause of moderate-to-severe pain in paediatric patients with CP.[15] In a study of secondary dystonia, defined as dystonia arising from an identified cause, of which 53% were classified as CP; caregivers perceived a worsening of dystonia over time in more than 50% of patients.[16] Dystonia can make caring for individuals with CP difficult, with challenges in dressing, feeding, and positioning. Musculoskeletal deformities were present in 50% of individuals with dystonia in CP by 5 years of age.[17]

Clinical management goals for dystonia in CP involve reducing dystonia to maximize function, decrease pain, or enhance ease of caregiving.[18,19] Management options include careful assessment and the initiation of goal-directed rehabilitation strategies, including physical or occupational therapy consultation; however, there is little evidence supporting these approaches.[20] Oral medications prescribed for individuals with dystonia in CP can include baclofen, benzodiazepines, clonidine, gabapentin, levodopa, trihexyphenidyl, and tetrabenazine. However, none is licensed for use in children and all are 'off label'.[19,21] An additional concern is the relatively high frequency of adverse drug reactions that result from using these medications.[22] Other available treatment options include botulinum toxin injections, intrathecal baclofen (ITB), and deep brain stimulation (DBS). The management of dystonia is complex and clinicians are currently challenged by a paucity of evidence or inconsistent evidence to inform management strategies.[18,19] The area would benefit from building consensus similar to the strong work completed through the National Institute for Health and Care Excellence establishing a pathway for spasticity for children and young people.[23]

Given the numerous options and complexity of managing dystonia in CP, the development of a care pathway integrating evidence and expert opinion would be useful in aiding clinicians in the clinical management of dystonia in CP. The American Academy of Cerebral Palsy and Developmental Medicine has defined a 'care pathway' as 'a practical summary, including an algorithm, of evidence informed guidelines or the best evidence, for an aspect of care/services for individuals with childhood-onset disabilities to inform clinical practice'.[24] The objective of this work was to systematically review the evidence for managing dystonia using pharmacological and/or neurosurgical interventions in individuals with CP, to inform this component of a Dystonia in CP American Academy of Cerebral Palsy and Developmental Medicine Care Pathway. In addition, the clinical context of the evidence was interpreted utilizing the international expertise of the clinician scientist author group (three paediatric neurologists, one developmental paediatrician, and one physiatrist all running large clinical hypertonia intervention programs including botulinum toxin, ITB, and DBS; and two physiotherapists with expertise in assessment and management of dystonia).

What this paper adds

- Intrathecal baclofen and deep brain stimulation are possibly effective in reducing dystonia.
- Current evidence does not support effectiveness of oral medications or botulinum toxin to reduce dystonia.
- Evidence is inadequate for pharmacological/neurosurgical interventions impact on improving motor function, pain/comfort, and easing caregiving.
- The majority of the care pathway rests on expert opinion.

METHOD

This systematic review was carried out according to the American Academy of Neurology Clinical Practice Guideline Process Manual and the 2015 amendments to these guidelines,[25,26] as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[27]

Criteria for literature search

A research librarian guided the primary search strategy for pharmacological and/or neurosurgical interventions for dystonia in CP. The primary search was aimed at identifying intervention articles for dystonia in CP by using intervention-specific keywords with a combination of keyword variations of dystonia and CP. The searched interventions included oral baclofen, benzodiazepines (clonazepam, diazepam, lorazepam), clonidine, gabapentin, levodopa, trihexyphenidyl, botulinum toxin, ITB, and DBS. A sample of the search strategy can be found in Table I. The inclusion criteria were as follows: (1) English-language full-text studies; (2) a minimum of five participants; and (3) a minimum of 50% of the participants diagnosed with dystonia in CP. However, studies that had less than 50% of the sample diagnosed with dystonia in CP (with >5 participants) were included only if results were presented for this subsample (i.e. one could interpret the results for only those participants with dystonia in CP). Computer-assisted literature searches were completed for articles published from 1945 to December 2015. The databases used in the literature search included: Ovid MEDLINE, CINAHL, AMED, Cochrane Reviews, Embase, and EBM Reviews. Citations from relevant systematic reviews were also consulted for eligible studies to include in this review.

Data extraction and classification process

After the databases were searched and duplications were removed, each article was reviewed (JS, IW) and data were extracted and classified independently by two reviewers (LB, AM). If required, a third independent reviewer (LS) was consulted to resolve any discrepant classifications. The extracted data included the study design, outcome measures, number, diagnoses, ages of participants, details of the studied intervention, results, and reported adverse events. After the first stage of classifications, the articles were reviewed again by an international expert panel comprised of two developmental paediatricians (DF, JR), three paediatric neurologists (J-PL, JWM, KH), and two paediatric physical therapists (EM, AH).

Table I: Systematic review search strategy and search date

Search	Keywords
Primary search strategy	dystoni*, cerebral pals*, involuntary movement disorder, hypertoni*, neurological hypertoni*
Benzodiazepines (29th January 2016)	Benzodiazepine*
Clonidine (29th January 2016)	Clonidine, catapres, kapvay, kapvay dose pack
Intrathecal baclofen (29th January 2016)	Intrathecal, baclofen, lioresal, gablofen, kemstro, gaba B agonist, pump
Oral baclofen (29th January 2016)	Oral, baclofen, lioresal, gablofen, kemstro, gaba B agonist
Clonazepam (29th January 2016)	Clonazepam, klonopin, klonopin wafer
Diazepam (29th January 2016)	Diazepam, valium
Lorazepam (29th January 2016)	Lorazepam, ativan
Trihexyphenidyl (29th January 2016)	Trihexyphenidyl, artane, trihexane
Levodopa (29th January 2016)	Levodopa, larodopa, dopar
Deep brain stimulation (1st February 2016)	Deep brain stim*, deep brain stimulation
Botulinum toxin (8th February 2016)	Botox injections, botulinum toxin, botulinum toxins, botulinum toxins type A
Gabapentin (1st January 2016)	Gamma-aminobutyric acid, gabapentin, pain, analgesics, gabapenti*, neuralgia, cyclohexanecarboxylic acids, neurontin, amines

An asterisk indicates an abbreviated keyword, which allowed for a broadened search of any variation of this word.

The articles were categorized into four hierarchical classes of evidence as outlined by the American Academy of Neurology.[25,26] To summarize, randomized controlled clinical trials and crossover studies that examined period and carryover effects were classified as class I. Beyond the American Academy of Neurology guidelines, we required a class I study to have a sample size of more than 20 participants. A study was designated class II if it lacked one criteria from class I or was a prospective cohort study. Controlled studies with objective outcomes were class III. Any articles that did not meet these criteria were considered class IV. Outcome measures from each article were grouped into four categories: (1) dystonia reduction; (2) improved motor function; (3) decreased pain/improved comfort; (4) improved ease of caregiving. When studies did not account for analysing multiple secondary outcomes, Bonferroni corrections were applied to determine overall statistical significance.

Within each of these four categories, recommendation levels were assessed as per American Academy of Neurology guidelines.[25,26] To summarize, a level A recommendation (effective or ineffective) required at least two consistent class I studies. Level B (probably effective or ineffective) required one class I study or at least two consistent class II studies. Level C (possibly effective or ineffective) required one class II study or at least two consistent class III studies. Level U indicates inadequate or conflicting data based on studies that did not satisfy class I to III requirements or included conflicting results. These recommendations were used to classify the level of evidence for the pharmacological and neurosurgical management of dystonia in CP.

RESULTS

A total of 1414 abstracts were initially identified through the search process. Of these, 203 were eliminated as duplications and 1211 articles were included for title and abstract review. In total, 798 articles were excluded after title and abstract review, leaving 413 articles to undergo full-text review. Twenty-eight articles fulfilled all the inclusion criteria and underwent data extraction (Fig. 1). The measures used to evaluate each outcome are summarized in Table II. There was one levodopa (Table SI, online supporting information), five trihexyphenidyl (Table SII, online supporting information), three botulinum toxin (Table SIII, online supporting information), six ITB (Table IV, online supporting information), and 13 DBS (Table SV, online supporting information) articles. No articles related to oral baclofen, benzodiazepines, clonidine, or gabapentin met the inclusion criteria for full-text extraction. Only studies graded as class I, II, or III were included in determining the level of evidence, as per the American Academy of Neurology guidelines. The results and levels of evidence for each intervention are summarized in Tables SI to SV. Studies with class IV evidence are indicated below the relevant table. A summary of the levels of evidence for all interventions are shown in Table III.

DISCUSSION

The clinical management of dystonia in CP is important as dystonia impairs motor function, causes pain, reduces daily activities, and makes caregiving challenging. The overall objective was to systematically review the evidence of pharmacological and neurosurgical interventions for the management of dystonia in CP. The majority of existing evidence focused on dystonia reduction as a primary outcome, with fewer studies evaluating the impact of pharmacological and neurosurgical dystonia interventions to improve motor function, reduce pain, and/or improve ease of caregiving. This is in contrast to what families have identified matters the most in terms of their priorities for clinical intervention, as described by a study of 273 caregivers of children with dystonia where pain (38%), difficulties in care-giving (24%), difficulty with hand use (22%), and seating (15%) were identified most commonly as the main concerns/priorities.[28]

The majority of the evidence in this review included children, adolescents, or young adults as the participants, with less available evidence on adults with CP. The sample sizes were generally small and studies seldom evaluated the long-term maintenance of effects. Overall, the results of this review identified a body of evidence that was limited, particularly for oral pharmacological management options

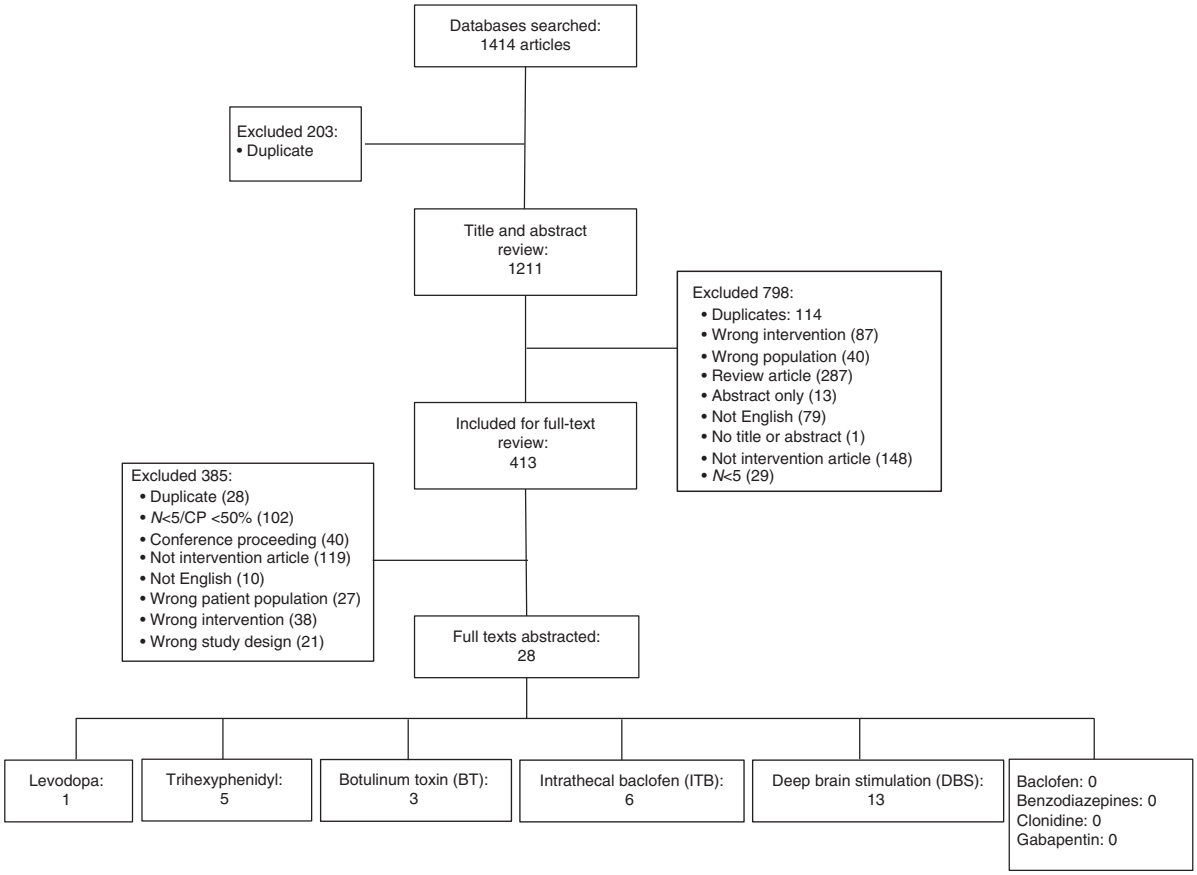

Figure 1: Systematic review article selection process. CP, cerebral palsy.

for dystonia in CP. This is in line with a systematic review on oral pharmacological treatments for dyskinetic CP that included dystonia or athetoid CP.[29] Possibly effective (level C) evidence was identified for the neurosurgical options of ITB and DBS to reduce dystonia. Current evidence does not support the use of oral medications or botulinum toxin to effectively reduce dystonia. There is no evidence or inadequate evidence for pharmacological and neurosurgical interventions to improve motor function, decrease pain, and improve ease of caregiving.

In comparing the state of the evidence for pharmacological and neurosurgical interventions for dystonia in CP to systematic reviews done for other forms of dystonia (e.g. primary genetic dystonias, cervical dystonia, blepharospasm) there is strong evidence for the effectiveness of botulinum toxin to improve cervical dystonia (level A or B depending on the type of botulinum toxin used) and blepharospasm (level B or C depending on the type of botulinum toxin used).[30] In a systematic review of primary dystonias and 'dystonia plus syndromes', DBS was found to be a good option for generalized dystonia or cervical dystonia after medication or botulinum toxin had failed.[31] It was reported that the response of primary dystonias to DBS was greater than secondary dystonias. A recent meta-analysis of DBS for primary dystonias identified significant improvements in dystonia scores with better outcomes associated with younger age at DBS surgery, early DBS intervention, and more severe dystonia at baseline.[32] Similar to our findings, there was little evidence to support oral pharmacological interventions in these broader 'dystonia' diagnostic conditions,[31,33,34] with the exception of one systematic review identifying level A evidence for the use of trihexyphenidyl to reduce primary torsion dystonia.[35] Given the differing responses of individuals to interventions with primary and secondary dystonia, it is important to highlight that generating and interpreting evidence specifically for dystonia in CP is of paramount importance.

Further discussion of each pharmacological and neurosurgical intervention, chosen for review because of their common use in clinical practice, is described below; outlining the mechanism of action, the evidence base, and recommendations where indicated, followed by the potential clinical context of the intervention, including potential adverse effects. Discussion in the 'clinical context' subsections reflects the expert opinion of the authors where evidence is not available.

Oral baclofen

Baclofen is an agonist at γ-aminobutyric acid $(GABA)_B$ receptors in the spinal cord and brain. $GABA_B$ receptors

Table II: Measurements used for outcome evidence evaluation

Outcome	Measures
Dystonia	• Burke–Fahn–Marsden Dystonia Rating Scale–movement (BFM-M) • Barry–Albright Dystonia Scale (BADS) • Modified Ashworth Scale (MAS) • Unified Dystonia Rating Scale-Upper Extremity (UDRS-UE) • Unified Parkinson's Disease Rating Scale (UPDRS-UE) • Abnormal Involuntary Movement Scale (AIMS)
Motor function	• Quality of Upper Extremity Skills Test (QUEST) • Melbourne Assessment of Unilateral Upper Limb Function (MAU) • Burke–Fahn–Marsden Dystonia Rating Scale-Disability (BFM-D) • Maximal pincher and grip strength • Box and blocks test • 9-hole peg test • Gross Motor Function Measure (GMFM) • Syllable repetition • Finger tapping, hand pronation, and supination • The Canadian Occupational Performance Measure (COPM; goal-specific for improved motor function) • Peak arm velocity of outward reaching
Pain/ comfort	• Paediatric Pain Profile (PPP) • The Short Form Health Survey (SF-36) • Symptom Checklist (SCL-90) • COPM (goal-specific for pain)
Caregiving	• Care and Comfort scale • COPM (goal-specific for improved ease of caregiving) • Goal Attainment Scaling (GAS) • Paediatric Quality of Life Measure (PQL)
Others	• Motor-evoked potentials (MEP) • H Reflex • Drooling scale

are metabotropic receptors linked via G proteins to voltage-sensitive potassium channels; activation of $GABA_B$ receptors results in inhibition. Oral baclofen is used commonly for the management of spasticity and primary dystonia.[36] However, it has not been studied systematically for the management of dystonia in CP. The search strategy yielded no studies of baclofen that met the inclusion criteria for managing dystonia in CP.

Recommendation

No recommendation can be made because no evidence is available.

Clinical context

Oral baclofen is commonly used in clinical practice by the clinical expert panel to manage dystonia in CP for generalized dystonia in CP causing pain or limiting activities. Oral baclofen is also used as a component of rescue treatment in the setting of acute baclofen pump failure. The chief adverse effects of baclofen are sedation, reduction of tone in axial muscles, urinary retention, and constipation.[37] In higher doses, it can lower the seizure threshold. If being used, titration of baclofen should be done slowly. Sudden withdrawal of baclofen can cause sustained muscle contraction leading to rhabdomyolysis with fever and mental status changes. Research evaluating the effectiveness of oral baclofen to manage dystonia in CP is clearly required.

Benzodiazepines

Benzodiazepines are a class of medications that act at the benzodiazepine receptor, which is linked to the $GABA_A$ receptor and potentiates the inhibitory postsynaptic action of GABA. Commonly used benzodiazepines include clonazepam, diazepam, and lorazepam. Specific benzodiazepines differ primarily in pharmacokinetics but not in their overall mechanism of action. Benzodiazepines are commonly used in the management of spasticity and for the management of seizures and anxiety.[38] They are also used by clinicians for management of dystonia; however, the search strategy revealed no studies of benzodiazepines for the management of dystonia in CP that met the inclusion criteria.

Recommendation

No recommendation can be made because no evidence is available.

Clinical context

Benzodiazepines are used in clinical practice by our clinical expert panel in the management of status dystonicus or dystonic storms,[12] including those related to acute failure

Table III: Summary of evidence levels of pharmacological and neurosurgical interventions

	Levodopa	Trihexyphenidyl	Botulinum toxin	ITB	DBS	Summary
↓ dystonia	No evidence	Level C (possibly ineffective)	Level U (inadequate data)	Level C (possibly effective)	Level C (possibly effective)	Support: ITB (level C) and DBS (level C); no support: trihexyphenidyl (level C)
↑ motor function	Level C (possibly ineffective)	Level C (possibly ineffective)	Level U (inadequate data)	Level U (inadequate data)	Level U (inadequate data)	Support: inadequate data; no support: levodopa (level C), trihexyphenidyl (level C)
↓ pain/↑ comfort	No evidence	Level U (inadequate data)	Level U (inadequate data)	No evidence	Level U (inadequate data)	Support: no evidence/inadequate data; no support: no evidence/inadequate data
↑ caregiving	No evidence	Level C (possibly ineffective)	No evidence	No evidence	Level U (inadequate data)	Support: no evidence/inadequate data; no support: trihexyphenidyl (level C)

ITB, intrathecal baclofen; DBS, deep brain stimulation.

of the baclofen pump or DBS and for short-term management of dystonia. The chief adverse effect is sedation, and in higher doses benzodiazepines depress respiratory drive.[39] Titration of benzodiazepines should be done gradually. Benzodiazepines demonstrate tachyphylaxis and tolerance such that increasing doses are often needed to provide sustained clinical benefit over time. Agitation before the next dose is frequently encountered with chronic benzodiazepine use. Sudden withdrawal of benzodiazepines can cause seizures, anxiety, dystonic storm, or a combination of both. Research is required to clarify the effectiveness and adverse effects including cognitive impact of benzodiazepines for dystonia in CP.

Clonidine

Clonidine is an α-adrenergic agonist. The use of clonidine in individuals with movement disorders has been largely directed towards tics,[40,41] but it is more commonly used for attention-deficit–hyperactivity disorder and disordered sleep management.[40] Lack of respiratory-depressant effects has favoured the use of clonidine sedation in intensive-care and high-dependency unit settings in individuals recovering from acute respiratory disorders and postoperative recovery form cardiopulmonary bypass procedures. In these circumstances, clonidine has largely replaced midazolam and morphine infusions to allow for swifter weaning from ventilation, as well as rapid weaning of clonidine where required.[42] Inadequate sedation in intensive-care/high-dependency units often results in extremely distressed individuals with extensor posturing and undirected thrashing of limbs reminiscent of acute dystonic crises. This has led to the increasing popularity of clonidine for severe dystonia, as graded by the Dystonia Severity Assessment Plan,[43] where, typically, the individual cannot tolerate sitting or sleep at night, or is decompensating towards frank status dystonicus. The search strategy revealed no studies of clonidine for the management of dystonia in CP.

Recommendation

No recommendation can be made because no evidence is available.

Clinical context

Clonidine is increasingly being considered in clinical practice for severe dystonia management in dystonic storms or disturbed sleep, alone or in combination with other medications in the outpatient or acute inpatient settings respectively.[44,45] However, clonidine is not yet routinely used by the majority of the clinical expert panel. Potential side effects include bradycardia, sedation, and hypotension.[46] More evidence for the efficacy and side effects of clonidine for dystonia are required, particularly opioid and benzodiazepine-sparing effects.

Gabapentin

Gabapentin, an analogue of GABA, was originally designed to be used as an anticonvulsant but gained popularity for reducing neuropathic pain.[47] The search strategy yielded no studies for the use of gabapentin for managing dystonia in individuals with CP. Despite this, it is increasingly being used in this population. A recent retrospective observational study analysed the use of gabapentin for severe dystonia as measured by the Dystonia Severity Assessment Plan in 69 children, 25 of whom had CP.[48] There was a significant decrease in the severity of dystonia and significant improvements were seen in sleep quality, sleep amount, mood and agreeableness, pain, general muscle tone, involuntary muscle contractions, and seating tolerance ($p<0.01$ in all areas). The study did not qualify for this review because less than 50% of participants had CP and the results of the CP group were not reported separately.

Recommendation

No recommendation can be made because no evidence is available.

Clinical context

Gabapentin is increasingly used in clinical practice by the expert clinical panel in dystonia in CP associated with pain. Generally there are few side effects, but it can cause somnolence (21% in drug vs 5% in placebo) and emotional lability (6% in drug vs 1.3% in placebo).[49] Stronger evidence for the effectiveness of gabapentin in dystonia in CP is needed.

Levodopa

Levodopa is a dopamine precursor that crosses the blood–brain barrier to produce central dopaminergic effects. It is typically administered with a dopa decarboxylase inhibitor to enhance the central effect and reduce unwanted peripheral side effects. Its signature use is in the treatment of dopa-responsive dystonia, which has led to interest in using it for secondary dystonia such as CP.[19] There is no evidence that individuals with dystonia in CP have a deficiency in dopaminergic transmission within the basal ganglia, unlike other disorders. This review identified a single randomized controlled trial with nine participants who did not achieve a significant change in upper extremity skills.[50] This corresponds with a level C (possibly ineffective) recommendation for improvement in motor function, with other domains (reduction in dystonia, improved pain/comfort, and ease of caregiving) not assessed.

Recommendation

Clinicians may choose not to prescribe levodopa to improve motor function in dystonia in CP (level C). There is insufficient evidence to make a recommendation on levodopa's effectiveness in reducing dystonia, decreasing pain, or easing caregiving.

Clinical context

There is widespread clinical use of levodopa when there is a high suspicion that an individual has dopa-responsive

dystonia as part of a diagnostic evaluation. However, the clinical expert panel does not use levodopa for routine use to reduce dystonia in CP owing to lack of perceived effectiveness.[51] Side effects can include somnolence, nausea, dyskinesias, and hallucinations.[52] Further research evaluating levodopa's role in the management of dystonia in CP is required.

Trihexyphenidyl

Trihexyphenidyl is a muscarinic receptor antagonist that acts on receptors throughout the body, including the central nervous system, to produce an anticholinergic effect. The direct mechanism of its effect in the central nervous system is unknown; however, it is postulated that rebalancing of cholinergic to dopaminergic interneuronal drive in the basal ganglia and associated structures leads to a reduction of dystonia.[53] Evidence for the effect of trihexyphenidyl on dystonia in this review is limited, with two studies using prospective or randomized controlled methods in a total of 42 study subjects. There is a level C (possibly ineffective) recommendation for reduction of dystonia, improvement in motor function, and ease of caregiving, and inadequate data for improved pain/comfort when using trihexyphenidyl in individuals with dystonia in CP. However, improvement in drooling was recorded in one of the two studies.[54]

Recommendation

Clinicians may choose not to prescribe trihexyphenidyl as it is possibly ineffective in reducing dystonia, improving motor function, and easing caregiving in dystonia in CP (level C). There was insufficient evidence to make a recommendation on trihexyphenidyl's effectiveness in improving pain and comfort.

Clinical context

Trihexyphenidyl is widely used in managing dystonia in CP in clinical practice by the clinical expert panel despite the limitations in the current evidence. Side effects related to general anticholinergic effects, such as constipation, blurred vision, dry mouth, and behavioural changes, are common and gradual dose escalation is important in reducing the likelihood of these adverse effects.[54,55] Additional research evaluating the role of trihexyphenidyl, including an assessment on the impact on cognitive function, in the management of dystonia in CP is required.

Botulinum toxin

Botulinum toxin temporarily inhibits the release of acetylcholine at the neuromuscular junction creating a focal chemodenervation at the injection sites. The flow of impulses is reduced, enabling the muscle to relax. This effect can be seen both in spastic and dystonic muscle. Despite frequent clinical use, there are few studies describing the effects of botulinum toxin in dystonia in CP. In the present review, there was inadequate data to support an effect on reducing dystonia, although a prospective study, with the less often used botulinum toxin type B, showed some support for reduction of dystonia.[56] This study also showed improvements in motor function in an arm-reaching task after injection of botulinum toxin in the elbow flexors. While some limited evidence showed some support for botulinum toxin in reducing pain and easing caregiving,[57] ultimately more research is necessary to show efficacy of botulinum toxin in reducing dystonia and improving pain/comfort and caregiving (level U).

Recommendation

No recommendation can be made because of insufficient evidence.

Clinical context

Botulinum toxin is a focal and reversible management that is commonly used in clinical practice and by the clinical expert team for treating focal and segmental dystonia. Potential adverse events are estimated to occur for less than 10% of post botulinum toxin injections in children with CP and include local or systemic weakness,[58] incontinence, dysphagia, or lower respiratory tract infections. As there is a risk of disturbing the balance over a joint with botulinum toxin, the clinical expert group often inject both flexors and extensors at a single-joint level. Further studies are warranted to gather information about the best use of botulinum toxin in dystonia in CP.

Intrathecal baclofen

ITB acts as an inhibitory $GABA_B$ agonist to decrease descending excitatory impulses. ITB reduces spasticity by binding to $GABA_B$ receptors in the dorsal spinal cord. However, for dystonia, it may also work at a central level with the exact mechanism still to be determined. The intrathecal versus oral administration facilitates higher baclofen cerebrospinal fluid levels as it bypasses the blood–brain barrier. In this review, there is level C (possibly effective) evidence for ITB in reducing dystonia. All studies showed an improvement in dystonia but one,[59] which provided a small dose of ITB as a single bolus. Two of the studies demonstrated persisting dystonia reduction over 12 to 24 months,[60,61] with evidence for enhanced dystonia reduction with a high catheter tip placement. There was inadequate data for ITB in improving motor control, improving pain/comfort, and easing caregiving.

Recommendation

Clinicians may choose ITB for dystonia reduction in individuals with CP with severe generalized dystonia (level C). There was insufficient evidence to make a recommendation for its use to improve motor control, relieve pain, or ease caregiving.

Clinical context

ITB is used in clinical practice by the clinical expert panel for consideration in the management of generalized dystonia not well controlled with oral medications and/or when dystonia creates challenges in pain/comfort or caregiving.

Side effects in the largest study of 86 individuals were found in 26% with constipation being the most common followed by decreased head control and drowsiness.[61] Surgical complications occurred in 38% with cerebrospinal fluid leaks, catheter problems, and infections reported. Further studies are required to evaluate the choice of ITB versus DBS in individuals with CP and severe generalized dystonia, although ITB is often considered over DBS in the presence of severe hypertonia where the tonal patterns are mixed with the presence of both dystonia and spasticity.

Deep brain stimulation

DBS neuromodulation of monogenetic dystonias represents a major advance in the management of these complex disorders.[62] DBS for 'secondary dystonias' of childhood and, in particular, dystonic CP, the major cause of dystonia in childhood, have consequently been of great clinical interest. This search identified 13 DBS studies, of which 12 of 13 were class III studies. Reduction of dystonia was reported in six of 12 class III studies,[63–68] whereas four of 12 failed to demonstrate dystonia reduction,[69–72] with one of these four negative studies evaluating adults only,[72] thus indicating that DBS could be possibly effective (level C) in reducing dystonia in CP. Evidence for DBS in improving motor function was conflicting. Three of 12 class III studies provided support,[64,66,68] whereas four of 12 class III studies showed no support for DBS improving motor function,[63,67,70,72] and one class III study identified mixed results with improvement in upper extremity motor function in the non-dominant hand but no change in the dominant hand.[73] Therefore, there was inadequate data to support improvement in motor function in dystonic CP. Reduction in pain or improvement in comfort was reported in two class III studies,[64,74] but two other class III studies failed to show a convincing reduction in pain,[66,70] so the evidence remains inadequate (level U). Only one class III study reported an improvement in ease of caregiving.[74]

Recommendation

Clinicians may choose DBS for dystonia reduction in individuals with CP who have severe generalized dystonia (level C). There was insufficient evidence to make a recommendation for its use in improving motor control, relieving pain, or easing caregiving.

Clinical context

DBS is used in clinical practice by the expert clinical panel for consideration in the management of generalized dystonia not well controlled with oral medications and/or when dystonia creates challenges in pain/comfort or caregiving. A recent evaluation of complications after DBS in 129 children in the UK over 3.3 years has shown an infection rate of approximately 10% across all age groups; however, it is lower (4.7%) in children younger than 7 years old implanted with rechargeable neurostimulators. Other side effects include electrode complications (18.4%) and the battery switching off unexpectedly (18.7%).[75] These sparse data, including a recent meta-analysis of DBS in CP,[76] nevertheless indicate that DBS neuromodulation could be beneficial for dystonic CP, but it must be emphasized that more studies, with larger numbers of cases with a more homogeneous age at DBS surgery and improved selection criteria, are needed to capture information relating to dystonia severity, pain, motor function, and caregiver burden, rather than focusing on dystonia reduction alone.[21,62,77,78] Studying the early provision of DBS in dystonic CP at a time when 'critical' and 'sensitive' windows for cerebral plasticity are still open may resolve the issue of whether better dystonia reduction, as well as better motor function and reduction in musculoskeletal deformity, can be achieved.[79]

Limitations

In addition to the under-recognition of dystonia in CP, particularly when it coexists with spasticity, this review was also limited owing to the difficulty in varied nomenclature of dystonia in CP over time (e.g. choreoathetotic, dyskinetic, extrapyramidal). It is possible that relevant literature that employed different terminology was not included. Additionally, the search may have been affected by the restriction to English-language studies. Owing to the heterogeneity of the studies with respect to outcomes and variation in reporting statistical results, we did not formally test for publication bias using tests such as funnel plots but expect that the possibility of a 'positive finding' publication bias may exist. However, these findings are broadly similar to a systematic review of the evidence supporting the management of acquired dystonia.[33] One treatment gaining popularity is the use of medical marijuana or cannabis.[80] However, via a systematic search, there is currently no specific evidence to support its use in dystonia in CP. Given the variability of international policies around this option, marijuana was not included in this evidence review.

CONCLUSION

In summary, a systematic review of the evidence for pharmacological and neurosurgical interventions for dystonia in CP has found that ITB and DBS are possibly effective (level C) in reducing dystonia. Current evidence does not support the effectiveness of oral medications or botulinum toxin in reducing dystonia and the use of these interventions is based on clinical expert opinion. There is generally inadequate evidence to evaluate the pharmacological and neurosurgical interventions' impact on motor function, pain relief, or ease of caregiving, as well as evidence guiding the sequencing or combining of therapies. The majority of the clinical use of these pharmacological and neurosurgical interventions rests on expert opinion with current evidence falling short in its ability to guide decision-making and practice. More research involving larger sample sizes and stronger study designs is required to fully inform the pharmacological and neurosurgical aspects of a

care pathway and improve the effectiveness of dystonia management in CP.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Levodopa intervention evidence
Table SII: Trihexyphenidyl intervention evidence
Table SIII: Botulinum toxin intervention evidence
Table SIV: Intrathecal baclofen intervention evidence
Table SV: Deep brain stimulation intervention evidence

REFERENCES

References marked with * are cited only in the Supporting Information.

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013; **28**: 863–73.
2. Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. *Mov Disord* 2010; **25**: 1538–49.
3. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Task Force on Childhood Motor Disorders. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics* 2003; **111**: e89–97.
4. Krägeloh-Mann IPU, Weber P. SCPE Reference and Training Manual (R&TM). Grenoble: Surveillance of Cerebral Palsy in Europe, 2005.
5. Reid SM, Carlin JB, Reddihough DS. Distribution of motor types in cerebral palsy: how do registry data compare? *Dev Med Child Neurol* 2011; **53**: 233–8.
6. Himmelmann K, Hagberg G, Uvebrant P. The changing panorama of cerebral palsy in Sweden. X. Prevalence and origin in the birth-year period 1999–2002. *Acta Paediatr* 2010; **99**: 1337–43.
7. Jethwa A, Mink J, Macarthur C, Knights S, Fehlings T, Fehlings D. Development of the Hypertonia Assessment Tool (HAT): a discriminative tool for hypertonia in children. *Dev Med Child Neurol* 2010; **52**: e83–7.
8. Lin JP, Nardocci N. Recognizing the common origins of dystonia and the development of human movement: a manifesto of unmet needs in isolated childhood dystonias. *Front Neurol* 2016; **7**: 226.
9. Rice J, Skuza P, Baker F, Russo R, Fehlings D. Identification and measurement of dystonia in cerebral palsy. *Dev Med Child Neurol* 2017; **59**: 1249–55.
10. Himmelmann K, Horber V, De La Cruz J, et al. MRI classification system (MRICS) for children with cerebral palsy: development, reliability, and recommendations. *Dev Med Child Neurol* 2017; **59**: 57–64.
11. Schlaggar BL, Mink JW. Movement disorders in children. *Pediatr Rev* 2003; **24**: 39–51.
12. Allen NM, Lin JP, Lynch T, King MD. Status dystonicus: a practice guide. *Dev Med Child Neurol* 2014; **56**: 105–12.
13. Bonouvrié LA, Becher JG, Vles JS, et al. Intrathecal baclofen treatment in dystonic cerebral palsy: a randomized clinical trial: the IDYS trial. *BMC Pediatr* 2013; **13**: 175.
14. Lubarr N, Bressman S. Treatment of generalized dystonia. *Curr Treat Options Neurol* 2011; **13**: 274–89.
15. Penner M, Xie WY, Binepal N, Switzer L, Fehlings D. Characteristics of pain in children and youth with cerebral palsy. *Pediatrics* 2013; **132**: e407–13.
16. Lin JP, Lumsden DE, Gimeno H, Kaminska M. The impact and prognosis for dystonia in childhood including dystonic cerebral palsy: a clinical and demographic tertiary cohort study. *J Neurol Neurosurg Psychiatry* 2014; **85**: 1239–44.
17. Lumsden DE, Gimeno H, Elze M, Tustin K, Kaminska M, Lin JP. Progression to musculoskeletal deformity in childhood dystonia. *Eur J Paediatr Neurol* 2016; **20**: 339–45.
18. Graham HK, Rosenbaum P, Paneth N, et al. Cerebral palsy. *Nat Rev Dis Primers* 2016; **2**: 15082.
19. Koy A, Lin JP, Sanger TD, Marks WA, Mink JW, Timmermann L. Advances in management of movement disorders in children. *Lancet Neurol* 2016; **15**: 719–35.
20. Stewart K, Harvey A, Johnston LM. A systematic review of scales to measure dystonia and choreoathetosis in children with dyskinetic cerebral palsy. *Dev Med Child Neurol* 2017; **59**: 786–95.
21. Koy A, Timmermann L. Deep brain stimulation in cerebral palsy: challenges and opportunities. *Eur J Paediatr Neurol* 2017; **21**: 118–21.
22. Lumsden DE, Kaminska M, Tomlin S, Lin JP. Medication use in childhood dystonia. *Eur J Paediatr Neurol* 2016; **20**: 625–9.
23. National Institute for Health and Care Excellence. Spasticity in children and young people overview. Available at: https://pathways.nice.org.uk/pathways/spasticity-in-children-and-young-people#content=view-info-category%3Aview-resources-menu (accessed 22 May 2017).
24. American Academy for Cerebral Palsy and Developmental Medicine. AACPDM Care Pathways. Available at: https://www.aacpdm.org/publications/care-pathways (accessed 24 May 2017).
25. Edlund W, Gronseth G, So Y, Franklin G. Clinical Practice Guideline Process Manual. St. Paul, MN: American Academy of Neurology, 2004: 1–57.
26. Gronseth GS, Cox J, Getchius TSD. Amendments to the 2011 American Academy of Neurology Clinical Practice Guideline Process Manual. St. Paul, MN: American Academy of Neurology, 2015.
27. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336–41.
28. Lumsden DE, Gimeno H, Tustin K, Kaminska M, Lin JP. Interventional studies in childhood dystonia do not address the concerns of children and their carers. *Eur J Paediatr Neurol* 2015; **19**: 327–36.
29. Masson R, Pagliano E, Baranello G. Efficacy of oral pharmacological treatments in dyskinetic cerebral palsy: a systematic review. *Dev Med Child Neurol* 2017; **59**: 1237–48.
30. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2016; **86**: 1818–26.
31. Albanese A, Barnes MP, Bhatia KP, et al. A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force. *Eur J Neurol* 2006; **13**: 433–44.
32. Moro E, LeReun C, Krauss JK, et al. Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. *Eur J Neurol* 2017; **24**: 552–60.
33. Heuvel CN, Tijssen MA, Warrenburg BP, Delnooz C. The symptomatic treatment of acquired dystonia: a systematic review. *Mov Dis Clin Prac* 2016; **3**: 548–58.
34. Snaith A, Wade D. Dystonia. *BMJ Clin Evid* 2014; **2014**: pii: 1211.
35. Balash Y, Giladi N. Efficacy of pharmacological treatment of dystonia: evidence-based review including meta-analysis of the effect of botulinum toxin and other cure options. *Eur J Neurol* 2004; **11**: 361–70.
36. He Y, Brunstrom-Hernandez JE, Thio LL, et al. Population pharmacokinetics of oral baclofen in pediatric patients with cerebral palsy. *J Pediatr* 2014; **164**: 1181–8.
37. Baclofen. Pediatric and Neonatal Lexi-Drugs. Hudson, OH, USA: Lexicomp Inc.: updated 13 November 2017,

cited 21 November 2017. Available from http://online.lexi.com. Subscription required to view.

38. Engle HA. The effect of diazepam (Valium) in children with cerebral palsy: a double-blind study. *Dev Med Child Neurol* 1966; **8**: 661–7.
39. Quality Standards Subcommittee of the American Academy of N, the Practice Committee of the Child Neurology Society, Delgado MR, Hirtz D, et al. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2010; **74**: 336–43.
40. Weisman H, Quereshi IA, Leckman JF, Scahill L, Bloch MH. Systematic review: pharmacological treatment of tic disorders—efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neurosci Biobehav Rev* 2013; **37**: 1162–71.
41. Singer S, Mink J, Gilbert D, Jankovic J. Movement Disorders in Childhood (2nd edition). Cambridge, MA: Elsevier Academic Press, 2016.
42. Arenas-López S, Riphagen S, Tibby SM, et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. *Intensive Care Med* 2004; **30**: 1625–9.
43. Lumsden DE, Lundy C, Fairhurst C, Lin JP. Dystonia Severity Action Plan: a simple grading system for medical severity of status dystonicus and life-threatening dystonia. *Dev Med Child Neurol* 2013; **55**: 671–2.
44. Sayer C, Lumsden DE, Kaminska M, Lin JP. Clonidine use in the outpatient management of severe secondary dystonia. *Eur J Paediatr Neurol* 2017; **21**: 621–6.
45. Nakou V, Williamson K, Arichi T, et al. Safety and efficacy of high-dose enteral, intravenous, and transdermal clonidine for the acute management of severe intractable childhood dystonia and status dystonicus: an illustrative case-series. *Eur J Paediatr Neurol* 2017; **21**: 823–32.
46. CloNIDine. In: Pediatric and Neonatal Lexi-Drugs. Hudson, OH, USA: Lexicomp Inc.: updated 8 November 2017, cited 21 November 2017. Available from http://online.lexi.com. Subscription required to view.
47. Lauder GR, White MC. Neuropathic pain following multilevel surgery in children with cerebral palsy: a case series and review. *Paediatr Anaesth* 2005; **15**: 412–20.
48. Liow NY, Gimeno H, Lumsden DE, et al. Gabapentin can significantly improve dystonia severity and quality of life in children. *Eur J Paediatr Neurol* 2016; **20**: 100–7.
49. NEURONTIN® (gabapentin) capsules, for oral use. Pfizer Labeling Parke-Davis. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=630#S6.1 (accessed 25 May 2017).
50. Pozin I, Bdolah-Abram T, Ben-Pazi H. Levodopa does not improve function in individuals with dystonic cerebral palsy. *J Child Neurol* 2014; **29**: 534–7.
51. Maas RPPWM, Wassenberg T, Lin JP, van de Warrenburg BPC, Willemsen MAAP. l-Dopa in dystonia: a modern perspective. *Neurol* 2017; **88**: 1865–71.
52. Carbidopa and Levodopa (Lexi-Drugs). In: Lexi-Drugs. Hudson, OH, USA: Lexicomp Inc.: updated 15 November 2017, cited 21 November 2017. Available from http://online.lexi.com. Subscription required to view.
53. Burke RE, Karanas AL. Quantitative morphological analysis of striatal cholinergic neurons in perinatal asphyxia. *Ann Neurol* 1990; **27**: 81–8.
54. Sanger TD, Bastian A, Brunstrom J, et al. Prospective open-label clinical trial of trihexyphenidyl in children with secondary dystonia due to cerebral palsy. *J Child Neurol* 2007; **22**: 530–7.
55. Rice J, Waugh MC. Pilot study on trihexyphenidyl in the treatment of dystonia in children with cerebral palsy. *J Child Neurol* 2009; **24**: 176–82.
56. Sanger TD, Kukke SN, Sherman-Levine S. Botulinum toxin type B improves the speed of reaching in children with cerebral palsy and arm dystonia: an open-label, dose-escalation pilot study. *J Child Neurol* 2007; **22**: 116–22.
57. Lundy CT, Doherty GM, Fairhurst CB. Botulinum toxin type A injections can be an effective treatment for pain in children with hip spasms and cerebral palsy. *Dev Med Child Neurol* 2009; **51**: 705–10.
58. O'Flaherty SJ, Janakan V, Morrow AM, Scheinberg AM, Waugh MC. Adverse events and health status following botulinum toxin type A injections in children with cerebral palsy. *Dev Med Child Neurol* 2011; **53**: 125–30.
59. Dachy B, Dan B. Electrophysiological assessment of the effect of intrathecal baclofen in dystonic children. *Clin Neurophysiol* 2004; **115**: 774–8.
60. Motta F, Stignani C, Antonello CE. Effect of intrathecal baclofen on dystonia in children with cerebral palsy and the use of functional scales. *J Pediat Orthop* 2008; **28**: 213–17.
61. Albright AL, Barry MJ, Shafton DH, Ferson SS. Intrathecal baclofen for generalized dystonia. *Dev Med Child Neurol* 2001; **43**: 652–7.
62. Cif L, Coubes P. Historical developments in children's deep brain stimulation. *Eur J Paediatr Neurol* 2017; **21**: 109–17.
63. Lumsden DE, Kaminska M, Gimeno H, et al. Proportion of life lived with dystonia inversely correlates with response to pallidal deep brain stimulation in both primary and secondary childhood dystonia. *Dev Med Child Neurol* 2013; **55**: 567–74.
64. Romito LM, Zorzi G, Marras CE, Franzini A, Nardocci N, Albanese A. Pallidal stimulation for acquired dystonia due to cerebral palsy: beyond 5 years. *Eur J Neurol* 2015; **22**: 426–e32.
65. Kim AR, Chang JW, Chang WS, Park ES, Cho SR. Two-year outcomes of deep brain stimulation in adults with cerebral palsy. *Ann Rehabil Med* 2014; **38**: 209–17.
66. Vidailhet M, Yelnik J, Lagrange C, et al. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. *Lancet Neurol* 2009; **8**: 709–17.
67. Marks W, Bailey L, Reed M, et al. Pallidal stimulation in children comparison between cerebral palsy and DYT1 dystonia. *J Child Neurol* 2013; **28**: 840–8.
68. Marks WA, Honeycutt J, Acosta F Jr, et al. Dystonia due to cerebral palsy responds to deep brain stimulation of the globus pallidus internus. *Mov Disord* 2011; **26**: 1748–51.
69. Olaya JE, Christian E, Ferman D, et al. Deep brain stimulation in children and young adults with secondary dystonia: the Children's Hospital Los Angeles experience. *Neurosurg Focus* 2013; **35**: E7.
70. Kim JP, Chang WS, Chang JW. Treatment of secondary dystonia with a combined stereotactic procedure: long-term surgical outcomes. *Acta Neurochir (Wien)* 2011; **153**: 2319–27.
71. Keen JR, Przekop A, Olaya JE, Zouros A, Hsu FP. Deep brain stimulation for the treatment of childhood dystonic cerebral palsy. *J Neurosurg Pediatr* 2014; **14**: 585–93.
72. Koy A, Pauls A, Flossdorf P, et al. Young adults with dyskinetic cerebral palsy improve subjectively on pallidal stimulation but not in formal dystonia, gait, speech, and swallowing testing. *Eur Neurol* 2014; **72**: 340–8.
73. Gimeno H, Lumsden D, Gordon A, et al. Improvement in upper limb function in children with dystonia following deep brain stimulation. *Eur J Paediatr Neurol* 2013; **17**: 353–60.
74. Gimeno H, Tustin K, Lumsden D, Ashkan K, Selway R, Lin JP. Evaluation of functional goal outcomes using the Canadian Occupational Performance Measure (COPM) following deep brain stimulation (DBS) in childhood dystonia. *Eur J Paediatr Neurol* 2014; **18**: 308–16.
75. Kaminska M, Perides S, Lumsden DE, et al. Complications of deep brain stimulation (DBS) for dystonia in children: the challenges and 10 year experience in a large paediatric cohort. *Eur J Paediatr Neurol* 2017; **21**: 168–75.
76. Koy A, Hellmich M, Pauls KA, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: a meta-analysis. *Mov Disord* 2013; **28**: 647–54.
77. Hudson VE, Elniel A, Ughratdar I, Zebian B, Selway R, Lin JP. A comparative historical and demographic study of the neuromodulation management techniques of deep brain stimulation for dystonia and cochlear implantation for sensorineural deafness in children. *Eur J Paediatr Neurol* 2017; **21**: 122–35.
78. Gimeno H, Lin JP. The International Classification of Functioning (ICF) to evaluate deep brain stimulation neuromodulation in childhood dystonia-hyperkinesia informs future clinical & research priorities in a multidisciplinary model of care. *Eur J Paediatr Neurol* 2017; **21**: 147–67.
79. Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: windows of opportunity in the developing brain. *Eur J Paediatr Neurol* 2017; **21**: 23–48.
80. Koppel BS, Brust JC, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014; **82**: 1556–63.

***81**. Hoon AH Jr, Freese PO, Reinhardt EM, et al. Age-dependent effects of trihexyphenidyl in extrapyramidal cerebral palsy. *Pediatr Neurol* 2001; **25**: 55–8.

***82**. Ben-Pazi H. Trihexyphenidyl improves motor function in children with dystonic cerebral palsy: a retrospective analysis. *J Child Neurol* 2011; **26**: 810–16.

***83**. Carranza-del Rio J, Clegg NJ, Moore A, Delgado MR. Use of trihexyphenidyl in children with cerebral palsy. *Pediatr Neurol* 2011; **44**: 202–6.

***84**. Arens LJ, Leary PM, Goldschmidt RB. Experience with botulinum toxin in the treatment of cerebral palsy. *S Afr Med J* 1997; **87**: 1001–3.

***85**. Albright AL, Barry MJ, Painter MJ, Shultz B. Infusion of intrathecal baclofen for generalized dystonia in cerebral palsy. *J Neurosurg* 1998; **88**: 73–6.

***86**. Zdolsek HA, Olesch C, Antolovich G, Reddihough D. Intrathecal baclofen therapy: benefits and complications. *J Intellect Dev Disabil* 2011; **36**: 207–13.

***87**. Albright AL, Barry MJ, Fasick P, Barron W, Shultz B. Continuous intrathecal baclofen infusion for symptomatic generalized dystonia. *Neurosurgery* 1996; **38**: 934–8.

***88**. Gimeno H, Tustin K, Selway R, Lin JP. Beyond the Burke–Fahn–Marsden Dystonia Rating Scale: deep brain stimulation in childhood secondary dystonia. *Eur J Paediatr Neurol* 2012; **16**: 501–8.