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Evidence Check

Paediatric deep brain stimulation

An **Evidence Check** rapid review brokered by the Sax Institute for the NSW Ministry of Health. October 2019.

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This report was prepared by:

Ann Scott, Joanna Duncan, David Tivey, Wendy Babidge (ASERNIP-S of the Royal Australasian College of Surgeons)

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Enquiries regarding this report may be directed to the:

Principal Analyst
Knowledge Exchange Program
Sax Institute
www.saxinstitute.org.au
knowledge.exchange@saxinstitute.org.au
Phone: +61 2 91889500

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Contents

Glossary of terms

Basal ganglia

The basal ganglia are deep-seated structures in the brain that are present in pairs, each having a right and a left side counterpart. The individual brain structures that make up the basal ganglia are called the caudate nucleus, putamen, globus pallidus, nucleus accumbens, subthalamic nucleus and substantia nigra.

Bilateral

Having or affecting two sides

Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)

This is a universally applied instrument for the quantitative assessment of dystonia in both children and adults.

Confidence interval (CI)

An estimated range of values that contains the true population value the study is intended to estimate; usually reported as a 95% CI, i.e., the range of values you can be 95% certain contains the true value for the population.

Deep brain stimulation (DBS)

A surgical procedure that uses electrical stimulation to deliver pulses to the brain; used to treat Parkinson's disease and other movement disorders such as dystonia and essential tremor

Dyskinesia

Abnormal movements that are disordered, impaired or excessive. The term may loosely imply various types of extra or abnormal movements that are generally fast. The term is also commonly used to denote abnormal movements that occur due to side effects of medications such as levodopa, a dopamine augmenting drug.

Dystonia

A neurologic movement disorder characterised by sustained muscle contractions, causing repetitive, patterned, involuntary, twisting or writhing movements and unusual posturing or positioning.

- Dystonia can be qualified as focal (affecting one part of the body, e.g. cervical dystonia), segmental (affecting one segment of the body, e.g. the right shoulder, arm and hand) or generalised
- Primary dystonia: This is an older term to denote dystonia that occurs in the absence of brain injury or visible abnormality on brain imaging
- Secondary dystonia: This is an older term to denote dystonia that occurs in the presence of brain injury or with visible abnormality on brain imaging

Dystonia-parkinsonism

A combination of dystonia and parkinsonism in which either type of movement problem may be more dominant than the other, or may follow the other with evolving disease course.

Globus pallidus

The globus pallidus is part of the basal ganglia deep within the brain. Specialised groups of nerve cells in the globus pallidus act as a relay system to process and transmit information from the basal ganglia, via the thalamus, to parts of the brain that regulate motor functions (e.g., the motor cortex). It is divided into two

parts: the globus pallidus externa and the globus pallidus interna (GPi). The GPi is a common target site for placing deep brain stimulation electrodes for dystonia.

Intrathecal infusion

Administration of a drug into the space filled with cerebrospinal fluid that lies between the thin layers of tissue covering the brain and spinal cord.

Levodopa

Levodopa is a drug used to treat Parkinson's disease and other neurological movement disorders such as dystonia and essential tremor.

Myoclonus

Sudden involuntary jerking of a muscle or group of muscles, which may be normal (e.g. a muscle jerk when falling asleep) or a result of an underlying disease.

Parkinsonism

A group of neurological disorders characterised by decreased body movement (hypokinesia), tremor and muscle rigidity

Prevalence

The total number of people with the disease at any one time.

Quality-adjusted life-year (QALY)

A measure of disease burden that takes into account the quantity and quality of life lived; it provides an indication of the benefits gained from a given therapy in terms of quality of life and survival for the patient.

Subthalamic nucleus (STN)

An oval mass of grey matter that is one of the pairs of structures that make up the basal ganglia. The subthalamic nuclei are located beneath a brain structure called the thalamus and are a common target site for placing deep brain stimulation electrodes for parkinsonism.

Abbreviations

The following abbreviations are used throughout this report:

BFMDRS	Burke-Fahn-Marsden Dystonia Rating Scale
BFMDRS-D	Burke-Fahn-Marsden Dystonia Rating Scale disability
BFMDRS-M	Burke-Fahn-Marsden Dystonia Rating Scale motor
CI	Confidence interval
DBS	Deep brain stimulation
FU	Follow up
GA1	Glutaric aciduria type 1
GMFM-88	Gross Motor Function Measure-88
GPi	Globus pallidus interna
HYS	Hoehn and Yahr Scale
IQR	Interquartile range
MPAN	Mitochondrial kinase-associated neurodegeneration
PKAN	Pantothenate kinase-associated neurodegeneration
QALY	Quality-adjusted life-year
SD	Standard deviation
SDy	Status dystonicus
STN	Subthalamic nucleus
SBRS	Subjective Benefit Rating Scale
UMRS	Unified Myoclonus Rating Scale

Executive summary

This Evidence Check rapid review was commissioned by the NSW Ministry of Health to review the evidence on deep brain stimulation (DBS) for paediatric patients with severe dystonia.

Background

Dystonia is characterised by sustained or intermittent repetitive, involuntary muscle spasms that result in unwanted abnormal movements, fixed postures or both. Paediatric dystonia may arise from a brain injury (acquired), a genetic mutation (inherited) or an unknown cause (idiopathic). Childhood-onset dystonia negatively affects growth, development and activity and can lead to progressive disability and deformity. Instances of uncontrolled, prolonged dystonia, known as status dystonicus or dystonic storm, can result in kidney damage, multiorgan failure and sometimes death.

There is no cure for dystonia, and its treatment in children is challenging because symptoms and treatment response can vary depending on a child's stage of development. Current best supportive care, which comprises pharmacological treatments and physiotherapy, is limited by low efficacy and high rates of adverse effects or both. As a result, DBS is increasingly being used to treat paediatric dystonia, sometimes as a first-line treatment option, even though there are no formal guidelines on its use for this indication.

Review questions

The aim of this rapid review was to assess the peer-reviewed literature published within the last 10 years with respect to the following questions:

1. Is paediatric DBS safe, efficacious and cost effective when compared with best supportive care?
2. Is DBS more safe or effective for some types of paediatric dystonia than others? Are there agreed patient selection criteria?
3. What models of care and service delivery or access and funding mechanisms are established to deliver paediatric DBS internationally?

Summary of methods

The peer-reviewed and grey literature was systematically searched to identify relevant studies and clinical practice guidelines or consensus statements published between January 2009 and June 2019. The reference lists of retrieved articles were also reviewed for potentially relevant studies. Abstract screening and study selection were conducted by one reviewer according to predefined inclusion and exclusion criteria. The methodological quality of the included studies was assessed using published quality assessment checklists, and the evidence base was classified using the National Health and Medical Research Council (NHMRC) dimensions of evidence. Data from the included studies were summarised narratively.

Sixteen papers met the inclusion criteria: one high quality systematic review, eight moderate- to high-quality case series studies, six case reports and one clinical practice guideline. The overall NHMRC evidence Grade was D (poor).

Key findings

Question 1

There were no studies identified that compared DBS with best supportive care in paediatric patients with dystonia. It is unlikely that trials comparing these two interventions will be forthcoming in the short- or

long-term, given the small number of patients affected and the ethical issues of performing comparative trials in this group.

Question 2

The evidence base comprised data on effectiveness outcomes for 457 patients and safety outcomes for 491 patients. With respect to the effectiveness of DBS for paediatric dystonia, generally consistent results from Level IV evidence suggested the following:

- The best responders to DBS in terms of improved motor function are patients with idiopathic dystonia or inherited dystonia without nervous system pathology
- Patients with inherited dystonia and nervous system pathology have comparatively lower, but still clinically significant, improvement in motor function, particularly those with pantothenate kinase-associated neurodegeneration or Lesch-Nyhan syndrome
- DBS is largely ineffective in improving motor function in patients with acquired dystonia, particularly those with dyskinetic cerebral palsy
- DBS may be an effective treatment for halting life-threatening status dystonicus, although the number of patients studied was small
- Other factors associated with a good response to DBS include older age at dystonia onset and truncal involvement
- Age and severity of dystonia at surgery do not appear to affect treatment response
- It is unclear whether improvements in motor function translate to better quality of life and overall health status.

With regard to the safety of DBS for treating paediatric dystonia, generally consistent results from Level IV evidence suggested the following:

- The DBS implantation procedure is relatively safe, although patients who have the electrode and impulse generator implanted in the same surgical session are more likely to experience a complication in the first six months than those who have two-stage surgery
- The total risk of a complication requiring surgical intervention is 8% per electrode-year. The most common complications that require additional surgery are hardware-related adverse events (range 17% to 26%) and surgical site infections (range 7% to 13%), which generally occur at least six months after the initial surgery
- Stimulation-induced side effects are rare, occurring in only 4% of patients
- The rates of adverse events do not differ among the dystonia subtypes
- Complications are most likely to occur in children aged 7–9 years and those with more severe dystonia.

Question 3

Aside from a single, outdated clinical practice guideline that made passing mention of the use of DBS in paediatric patients with dystonia, no information was identified on service delivery models or funding mechanisms for paediatric DBS.

Gaps in the evidence

There was limited evidence for Questions 1 and 3. For research Question 2, the evidence base was impacted by the limitations inherent in retrospectively-collected data. Although the evidence for DBS in paediatric inherited and idiopathic dystonia is promising, many questions remain. Data are sparse for patients with acquired dystonia and its numerous aetiologies, and the effects of high-frequency neuromodulation on a maturing brain are not yet known. It is also unclear how DBS affects pain, mood, quality of life and overall health status, and whether there is an optimal implant site for each dystonia subtype. The economic impact of a treatment begun in childhood that requires lifelong maintenance and follow-up also needs to be

assessed. Data from two recently established prospective multicentre registries are likely to help bridge some of these knowledge gaps.

Discussion of key findings

Adequately assessing the effectiveness of DBS in children and adolescents is challenging. Many of the commonly used measures of dystonia impairment, some of which are designed for use in adults, do not capture more subjective factors such as wellbeing, quality of life and disease burden. Consequently, most studies do not measure what matters most to children and their families. Future studies should include severity scales and measures of quality of life, autonomy and pain in accordance with the World Health Organization's International Classification of Functioning, Disability and Health. It is also important that studies have an adequate follow-up period, since the effects of DBS may be cumulative and could take at least one year to stabilise in certain patient groups.

Conclusion

DBS has been used in children and adolescents with medically refractory idiopathic dystonia and inherited dystonia without nervous system pathology for more than a decade. The growing body of Level IV evidence generally supported this practice for improving motor function and disability, although more data need to be collected on other aspects of patient wellbeing such as quality of life, cognitive function, pain and autonomy. Patients with medically refractory inherited dystonia with nervous system pathology may also benefit from DBS, but it is not yet clear which aetiologies within this subgroup would achieve the most improvement from the treatment. DBS should also be considered for the emergency treatment of paediatric patients experiencing medically refractory, life-threatening status dystonicus.

While DBS is generally well tolerated, it is associated with complications that may require repeat surgery, and it requires ongoing, lifelong maintenance and follow-up from specialised providers.

Background

This Evidence Check rapid review was commissioned by the NSW Ministry of Health to review the evidence on deep brain stimulation (DBS) for paediatric patients with severe dystonia. The rapid review focused on the clinical effectiveness, safety and cost-effectiveness and patient tolerability of DBS, particularly with respect to the different dystonia subtypes.

The NSW Ministry of Health will use this Evidence Check to guide further decision making in health service prioritisation and planning for the treatment of paediatric dystonia in NSW.

Dystonia in childhood and adolescence

Dystonia is a relatively common neurological condition characterised by sustained or intermittent repetitive, involuntary muscle spasms or stiffening that typically occur during attempted activity and result in unwanted abnormal movements, fixed postures or both.[1-3] It can manifest in a specific part of the body (focal dystonia) or affect multiple muscle groups throughout the body (generalised dystonia), and may occur in isolation (isolated dystonia) or in conjunction with other movement disorders (combined dystonia) such as parkinsonism and myoclonus.[4] Depending on the body area affected, the muscle spasms can be painful and can severely impair an individual's ability to eat, speak or walk.[5, 6] Childhood-onset dystonia also negatively affects growth, development, education and activity, and can lead to progressive disability and deformity.[3]

Instances of uncontrolled, prolonged dystonia, known as status dystonicus or dystonic storm, are a medical emergency. Status dystonicus may occur spontaneously or, in the case of certain dystonia typologies, be triggered by an infection, medication or voluntary movement.[7] The intense, unremitting muscle contractions can cause breakdown of skeletal muscle and release of myoglobin into the bloodstream (rhabdomyolysis), which can result in kidney damage, multiorgan failure and death (in up to 10% of patients).[6-8]

While the cause of dystonia is not fully understood, it is generally thought to result from abnormal functioning of the basal ganglia in the brain.[2, 9] The younger a person is at symptom onset, the more likely the muscle spasms will spread to other parts of the body.[4] Dystonia is classified according to three main factors: the age at which symptoms develop; the areas of the body affected; and the underlying cause or aetiology (acquired, inherited or idiopathic) (See Table 1).[7]

Acquired dystonia is the most common form of dystonia in the paediatric population.[2, 10] In these cases, damage to the brain's motor network may arise from various causes including stroke, drug toxicity, metabolic disturbances, poisoning, infection, autoimmune disorders, cortical maldevelopment, trauma, neoplasms, neurodegenerative disease and perinatal hypoxia. Children with acquired dystonia often have seizures or other neurodevelopmental disabilities.[6, 11] Dyskinetic cerebral palsy, which is characterised by uncontrolled, abrupt twisting movements, is the most common cause of acquired dystonia in children and adolescents.[11, 12] The prevalence of cerebral palsy is 1.7 to 3.1 per 1000 live births in high income countries, and the dyskinetic form accounts for up to 15% of these cases.[7, 13]

Most inherited dystonias become apparent before the teenage years (mean age at onset is 12 years), starting in one muscle group and progressively spreading to other parts of the body with increasing age, often severely limiting function. Patients typically have normal intellect, but their ability to communicate may be impaired.[64, 7] A type of dystonia called DYT1 early-onset dystonia, caused by a mutation in the *TOR1A* gene, is the most common inherited dystonia in children. It occurs in 1 in 160,000 children worldwide and accounts for 16% to 53% of paediatric-onset dystonia in non-Jewish populations. The prevalence in Ashkenazi Jewish populations is 1 in 3000–9000..[4, 7, 14]

Table 1: Current classification of dystonia[1, 15]

Dystonia Type	Examples	Previous Terminology
Inherited Without nervous system pathology	DYT1 DYT6 Myoclonus-dystonia Segawa syndrome	Primary dystonia Dystonia-plus
Inherited With nervous system pathology	Pantothenate kinase-associated neurodegeneration Glutaric aciduria type 1 Methylmalonic acidemia Batten disease	Secondary dystonia Heredodegenerative dystonia
Acquired	Cerebral palsy Kernicterus Stoke Traumatic brain injury	Secondary dystonia
Idiopathic (unknown cause)	Sporadic Familial with no known genetic cause	Primary dystonia

Current treatments

There is no cure for dystonia, and treatment options are restricted by the limited understanding of its aetiology and pathogenesis.[3] Treating dystonia in children is challenging because their physiological, cognitive and neuromuscular states vary with developmental stage, which can markedly affect disease manifestation and treatment response.[3, 7] Current treatments for paediatric dystonia aim to increase function and quality of life by improving movement and posture, and are primarily based on extrapolation of data from clinical trials in adults.[3, 7]

There are several pharmacological treatments for dystonia symptoms, including anticholinergic drugs, dopamine augmenting or suppressing agents, baclofen and benzodiazepines (usually in combination with other drugs such as baclofen).[4, 6] The most common first-line treatment for segmental and generalised dystonias is high-dose trihexyphenidyl (an anticholinergic drug), but its efficacy is poorly documented in children and some studies have shown that children with dyskinetic cerebral palsy experience worsening of symptoms.[7, 14, 16] The side effects of anticholinergics include memory loss, confusion, restlessness, depression, dry mouth and constipation.[17]

Botulinum toxin injections, which act locally and have fewer side effects than many systemic drugs, are used to reduce disabling focal symptoms. However, repeat injections, for which children need sedation or anaesthesia, are usually required every three to four months and the treatment is of limited use in generalised dystonia.[4, 7] Other drugs such as benzodiazepines, anticonvulsants and dopamine augmenting or suppressing agents may provide benefit in select patient groups, but their use is generally limited.[4] For example, levodopa (a dopamine augmenting drug) is very effective in relieving symptoms of dopamine-responsive dystonia (Segawa syndrome), a rare genetic disorder that causes defects in dopamine synthesis, although the side effects include anorexia, nausea, vomiting, constipation, sedation, hallucinations, and dyskinesia.[14, 18]

Continuous intrathecal infusion of baclofen (a muscle relaxant drug) via a mini pump implanted under the abdominal fascia is used for generalised dystonia when oral medications have failed, particularly in children who have dystonia and spasticity.[14] Although baclofen has been shown to reduce spasticity in children with cerebral palsy[19], its effectiveness in reducing dystonic symptoms is less established.[20, 21] The most common

side effects are sedation and nausea, but abrupt withdrawal, due to catheter malfunction or missed pump refilling, can cause psychosis and life-threatening seizures.[12, 17, 18]Supportive therapies, such as physiotherapy and occupational therapy, are often used in combination with pharmacological treatments, but the benefits, if any, are often short-lived.[17, 22]

Overall, the current treatments for childhood dystonia are limited by low efficacy, high rates of adverse effects or both.[23] In addition, while these treatments may reduce the symptoms of dystonia, they do not necessarily improve functional independence.

Deep brain stimulation (DBS)

The limited treatment options for children with dystonia have led to interest in the use of DBS for medically refractory cases. DBS or neuromodulation uses high-frequency electrical impulses to block or modify the irregular neuronal activity of the damaged brain region that causes dystonia.[24]

The DBS device is composed of a pulse generator and two electrode leads. With the patient under general anaesthesia, tiny wire electrodes are inserted through small burr holes in the scalp into one or both sides of the brain's basal ganglia under magnetic resonance imaging (MRI) guidance. At the same time, or in a separate procedure, a battery-powered pulse generator is implanted under the skin of the abdomen or below the collarbone. The electrodes are connected to the pulse generator by insulated wires passed under the skin down through the neck, and the amount of stimulation is adjusted according to symptoms.[18, 24, 25] Since childhood dystonia is often generalised, the DBS electrodes are usually implanted bilaterally, most commonly in the globus pallidus internus (GPi). However, the subthalamic nucleus (STN) and thalamus are also sometimes targeted. The pulse generator batteries can be recharged by the patient at home using a wearable recharging system, which means they may not need to be surgically replaced for up to 15 years.

Although there are no formal guidelines on indications for DBS in paediatric dystonia, there is a general consensus that DBS therapy is useful as an option for primary generalised dystonia that is not readily treated with medication. It is considered less useful in children with secondary dystonia because of the extensive brain injury that is usually present.[4, 18] Since optimal DBS stimulator settings for the various dystonia types are not well established, frequent visits are often required to adjust settings, and benefits from surgery may not be seen for weeks or even months.[17] Although DBS is reversible, it is nonetheless a life-long therapy that requires ongoing maintenance and follow-up.[18] Its safety in children is unclear, and its effects on the developing brain and musculoskeletal system and the natural course of disease are unknown.[3, 13]

The aim of this rapid review was to assess the peer-reviewed literature published within the last 10 years on the safety, clinical efficacy and cost-effectiveness of DBS for paediatric patients with dystonia. Information was also sought on optimum methods for providing DBS services to patients with paediatric dystonia.

Methods

The aim of this rapid review was to address the following questions:

1. Is paediatric DBS safe, efficacious and cost effective when compared with best supportive care?
2. Is DBS more safe or effective for some types of paediatric dystonia than others? Are there agreed patient selection criteria?
3. What models of care and service delivery or access and funding mechanisms are established to deliver paediatric DBS internationally?

Study selection

A systematic literature search was conducted to identify relevant studies published between 1 January 2009 and 12 June 2019 (See Appendix 1). The search was developed and conducted prior to the study selection process. The reference lists of retrieved articles were also reviewed for potentially relevant studies.

Titles and abstracts were screened by one reviewer and full-text publications of potentially relevant articles were retrieved to determine their eligibility according to the predefined selection criteria listed in Table 2.

Primary and secondary research evidence

A best available evidence approach was used to select studies. Secondary research, such as systematic reviews and health technology assessments, was preferentially included. Where there were two or more systematic reviews with identical comparators and patient populations, only the most recently published systematic review was included unless it was less comprehensive than the earlier review or an earlier review presented a novel analysis of the evidence base. Eligible primary research published after the search end date of the most recent systematic review was also included.

An article was deemed to be a systematic review if it met all of the following criteria: [26]

- Focused clinical question
- Explicit search strategy
- Use of explicit, reproducible and uniformly applied criteria for article selection
- Critical appraisal of the included studies
- Qualitative or quantitative data synthesis.

If no suitable systematic reviews on the topic were available, eligible primary studies were selected for inclusion. When overlapping patient groups were reported in studies, only the paper quoting the most complete data set was used.

Studies were excluded if they: were included in a selected systematic review; were duplicate or preliminary results; reported combined data from different populations and results for the population of interest could not be disaggregated; were narrative reviews, editorials, study protocols or conference abstracts; or could not be retrieved during the review period. Studies published prior to the literature search end date of the most recent included systematic review were also excluded.

Table 2: Study inclusion criteria (PICO format)

Population	Paediatric patients (≤20 years) encompassing the following age subcategories as per Albanese et al.[1]: • Infancy (birth to 2 years) • Childhood (3–12 years) • Adolescence (13–20 years)
Intervention	Deep brain stimulation
Comparators	Conventional best supportive care (medications and/or physiotherapy)
Outcomes	Safety: Adverse effects, unintended consequences Efficacy: Including, but not limited to movement severity, quality of life or functional outcomes measured preoperatively and postoperatively with an objective rating scale (e.g. Barry-Albright Dystonia Scale[27], Burke-Fahn-Marsden Dystonia Rating Scale[28], Unified Myoclonus Rating Scale[29], Canadian Occupational Performance Measure[30], Subjective Benefit Rating Scale[31])[a] Effects on family/carers Direct or indirect costs
Study design	*Questions 1 & 2*: Systematic reviews with or without meta-analyses, health technology assessments, interventional studies of any design, qualitative studies, cost-effectiveness or other cost analyses and clinical practice guidelines *Question 3*: Clinical practice guidelines; other articles or studies of any design that contain information on models of care and service delivery or access and funding mechanisms for paediatric deep brain stimulation
Publication date	2009 onwards
Language	English only

Note: PICO = Population, Intervention, Comparator and Outcome

[a]Studies evaluating DBS in patients with status dystonicus that did not use an objective rating scale were included if they reported on resolution or recurrence of status dystonicus

Clinical practice guidelines

An article was deemed to be a clinical practice guideline if it met all of the following criteria:

- It contained the word "guideline" or "recommendation" in its title or introduction, or contained recommendations on the use of DBS for paediatric dystonia
- It was developed by at least two authors
- It was evidence-based.

Although clinical practice guidelines that were not evidence based (e.g. consensus statements containing recommendations based only on expert opinion) were originally excluded, this criterion was overridden given the lack of such guidelines available.

Evidence grading and quality appraisal

The quality of a study refers to the extent to which it is has been designed and conducted to reduce bias in the estimation of outcomes. One reviewer assessed the methodological quality of the included studies. Systematic reviews were appraised with the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) tool.[32] AMSTAR is a 16-item checklist that assesses systematic reviews for quality of reporting and potential biases in methodology and execution. Case series studies were assessed with a quality assessment checklist

developed by the Institute of Health Economics.[33] This 20-item tool appraises the quality of the study's design, reporting, measurement of outcomes and data collection and analysis. The checklist was modified by removing item 11, which pertains to whether outcome assessors were blinded to the intervention received, because this is not applicable for patients receiving DBS. The quality of case reports and studies included in a selected systematic review was not assessed. Quality assessment results were not used to include or exclude studies.

The evidence presented in the selected studies was classified using the dimensions and levels of evidence defined by the National Health and Medical Research Council (NHMRC).[34, 35] These dimensions consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence.

Data extraction

Data were extracted by one reviewer using predetermined data extraction forms. Information extracted from health technology assessments and systematic reviews included: the studies reviewed; funding sources and conflicts of interest; inclusion and exclusion criteria; interventions; outcome measures; and relevant results and conclusions. For primary studies, extracted information included: publication and study characteristics; funding sources and conflicts of interest; study population and intervention details; type of outcomes reported; and relevant qualitative and quantitative results. Information extracted from clinical practice guidelines included guideline profile information (title, country, condition and intended users), the relevant recommendations and noted evidence gaps. Study authors were not contacted for additional data.

Results were only extracted if they were stated in the text, tables, graphs or figures of the article, or could be accurately extrapolated from the data presented. If no data were reported for a particular outcome, in particular adverse effects, then no value was tabulated. This was done to avoid the bias caused by incorrectly assigning a value of zero to an outcome measurement on the basis of an unverified assumption. For example, a zero rate for intraoperative complications was only tabulated if it was specifically stated in the study text that no intraoperative complications occurred in the patient sample.

Data from the included studies were summarised narratively. No statistical pooling of outcome data was performed.

Included studies

A total of 951 potential studies were located during the literature database search, with an additional five records identified by the grey literature search. After title and abstract screening, 75 full-text articles were retrieved. On closer examination, 16 records met the eligibility criteria and were included as shown in Figure 1. A summary table of the included studies is provided in Appendix 2.

In total, one systematic review[15] was included plus eight case series studies[36-43] and six case reports[44-49] published after the systematic review, all of which represented level IV evidence. The systematic review by Elkaim et al.[15] summarised data on the effectiveness of DBS for 321 paediatric patients with dystonia from 72 unique primary studies (level IV evidence); the median follow up ranged from 11 to 20 months.

Four case series studies[37-39, 42] and four case reports[44, 47-49] published after Elkaim et al.[15] documented safety and effectiveness outcomes in a total of 151 patients (range 4–19 years) receiving DBS for various dystonia aetiologies. Bilateral DBS of the GPi was undertaken in 92% of patients, with a postoperative follow up ranging from six months to a mean of 4.6 years.

Five case series studies[36, 37, 40, 41, 43] and two case reports[45, 46] described safety and effectiveness outcomes for 16 patients (range 6–15 years) with various dystonic aetiologies who received DBS for status dystonicus. The primary target for bilateral DBS was GPi in 89% of patients. Postoperative follow up ranged from six months to 10 years.

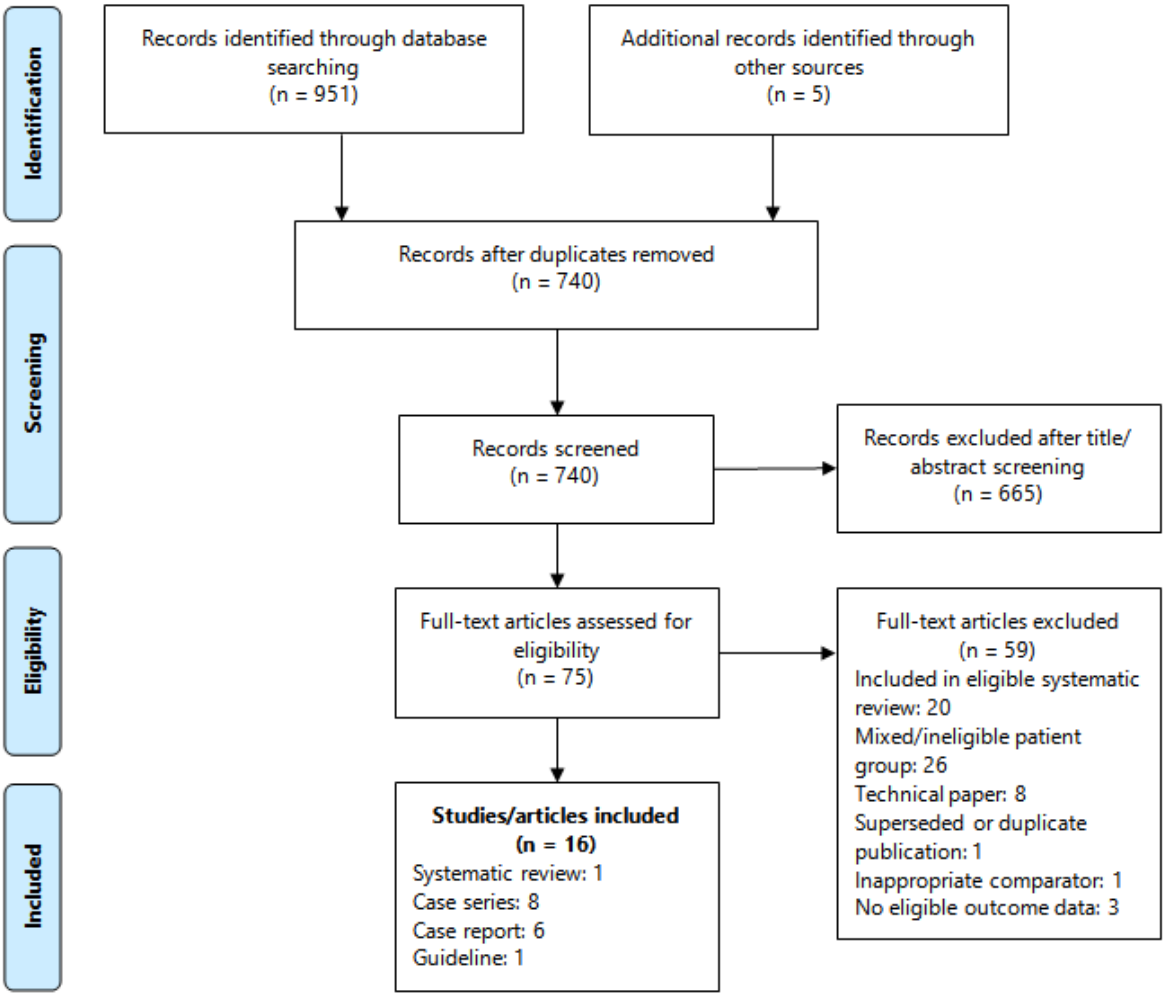

Figure 1: Selection process for identifying relevant papers on DBS for paediatric dystonia

Effectiveness outcome data

The systematic review by Elkaim et al.[15] focused exclusively on the effectiveness of DBS for paediatric dystonia. It included 72 unique primary studies published from January 1999 to August 2017. In accordance with current best practice for incorporating existing systematic reviews into new reviews,[50] the results of Elkaim et al.[15] were summarised (the full texts of the primary studies were not retrieved). The evidence base was then updated by including all relevant studies published from August 2017 to the current date. Therefore, the evidence base for effectiveness in this Evidence Check covers the time period from January 1999 to June 2019 and comprises one systematic review, eight case series studies[36-43] and five case reports.[45-49]

Safety outcome data

Since safety was not the primary focus of the systematic review by Elkaim et al.[15], complication rates were not analysed in detail. Therefore, the full-texts of all studies (both included and excluded) cited in Elkaim et al.[15] that were published from 2009 onwards were retrieved. Where available, safety data were extracted from studies that met the inclusion criteria for this rapid review (See Figure 2). This evidence was then updated by including all relevant studies published from August 2017 to the current date. Therefore, the evidence base for safety covers the time period from January 2009 to June 2019 and comprises 24 case series studies and case reports sourced from Elkaim et al.[15] plus seven case series studies[36-39, 41-43] and four case reports[44-46, 48] published since August 2017.

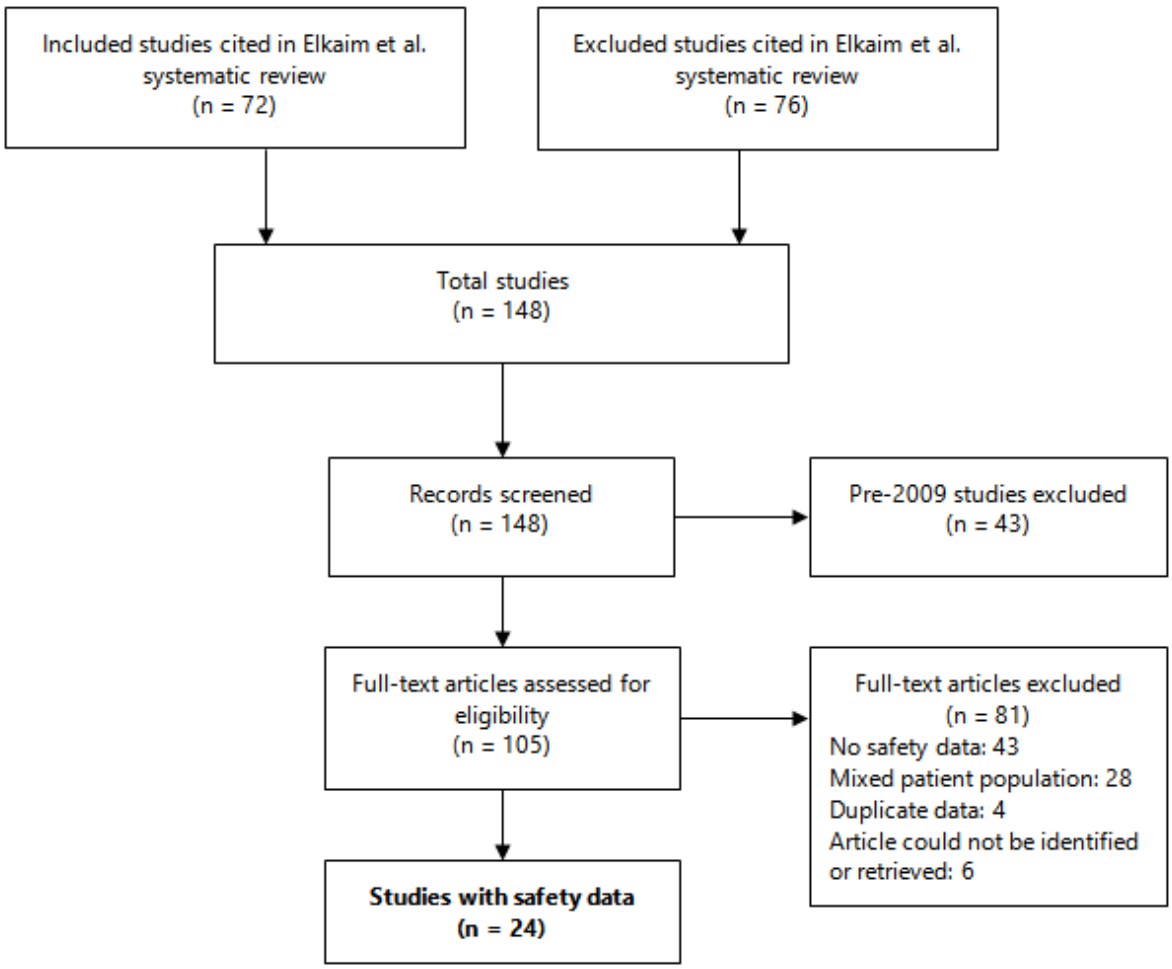

Figure 2: Selection process for identifying relevant studies cited in Elkaim et al.[15] that reported safety outcomes

Other outcome data

There were no studies identified that analysed the cost effectiveness of DBS for paediatric dystonia.

A single guideline was identified that made recommendations on patient selection for DBS with some reference to paediatric patients with dystonia.[51]

There were no articles identified that contained information on models of care and service delivery or access and funding mechanisms for paediatric DBS.

Findings

In each section, evidence from secondary sources (systematic reviews) is presented first, followed by findings from primary data sources.

Quality appraisal results

Quality appraisal results are provided in Appendix 3.

The included systematic review[15] only represented level IV evidence because the evidence base comprised solely case series and case reports. However, its overall quality of conduct and reporting was high, as rated by AMSTAR 2, indicating that it is an accurate and comprehensive summary of the results of the available studies. The review conducted a comprehensive literature search, provided sufficient descriptions of study characteristics and inclusion criteria, pooled study results using an appropriate method, provided a list of excluded studies, synthesised the data appropriately and had no notable conflicts of interest. The only non-critical weakness was that it did not provide information on the conflicts of interest of the included primary studies.

The quality of reporting was relatively high among the included case series studies (level IV evidence), indicating a relatively low risk of bias (Figure 3). Six[36-39, 41, 42] of the eight studies fulfilled at least 13 of the 19 quality criteria, with the other two[40, 43] satisfying nine criteria. The studies all clearly described participant characteristics and inclusion criteria as well as the reasons for losses to follow up, when they occurred. Most of the studies measured outcomes and analysed the results appropriately. The main weaknesses were that the majority of studies relied on retrospective data collection (only one study[38] had definitely prospective data collection), and 63% were from single centres and did not appear to have included consecutive patients. In addition, not all of the studies were able to include patients at a similar point in their disease status, and only half of the studies had an adequate follow-up length (≥ one year). However, many of these issues are likely related to the rarity of the condition and the highly specialised nature of the treatment being assessed, rather than a deficiency in study execution. None of the studies had any notable conflicts of interest that were likely to bias the results.

Question 1: Safety, effectiveness and cost effectiveness of DBS compared with best supportive care

There were no comparative studies identified that compared paediatric DBS with best supportive care.

Question 2a: Effectiveness of DBS for the various types of paediatric dystonia

Effectiveness data from the systematic review are provided in Appendix 2, Table 2.1. Effectiveness data from the primary studies are provided in Appendix 4.

Elkaim et al.[15] included 72 unique case series or case reports (level IV evidence) on DBS in 321 children or adolescents with dystonia of various aetiologies. In 12 of these patients, the diagnosis was either not stated or was not recognised as having an aetiological link to dystonia. The combined Burke-Fahn-Marsden Dystonia Rating Scale[28] motor (BFMDRS-M) subscores for all dystonia types improved by a median 42% (interquartile range [IQR] 12%-80%), with 86% of the 321 patients noting some improvement over their preoperative state at the last follow-up (median 12 months). Clinically significant (≥20%) improvement was recorded in 66% of patients. The median improvement in BFMDRS disability (BFMDRS-D) subscores was 28% in the 218 patients for whom this score was reported separately.

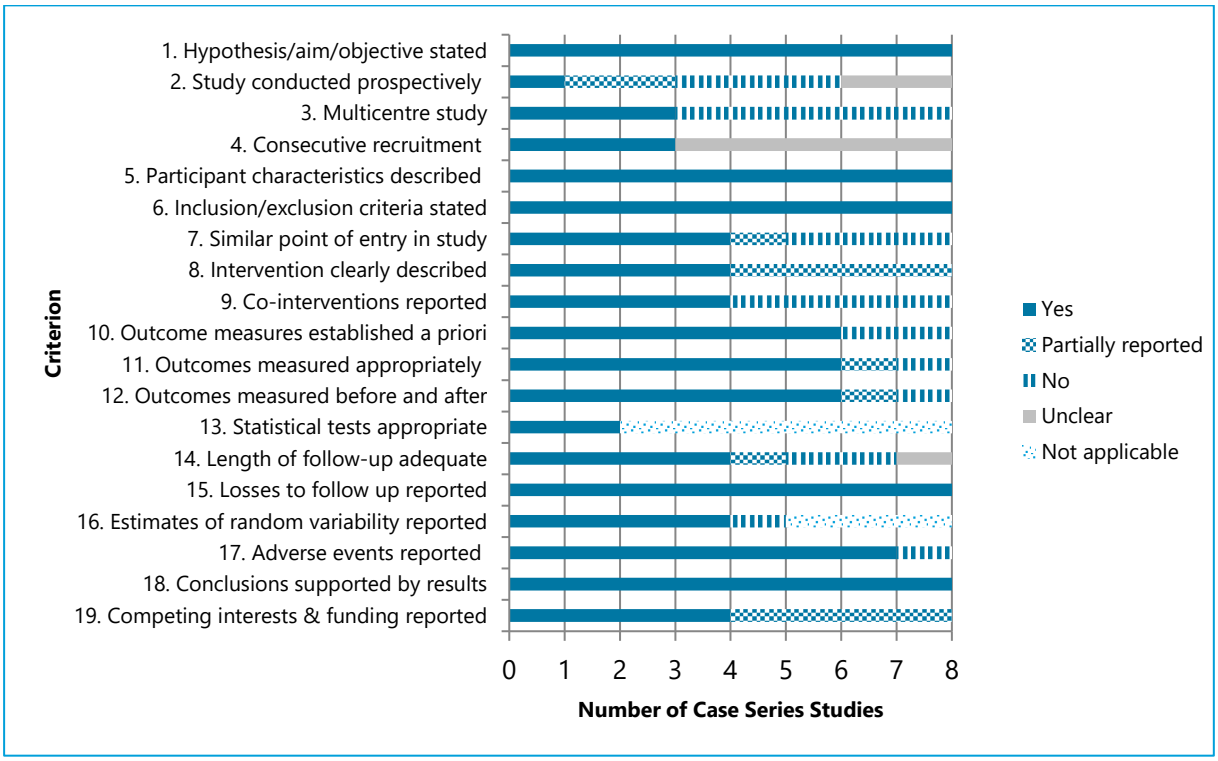

Figure 3: Quality appraisal results for included case series studies using the case series checklist[33]

The findings on the effectiveness of DBS to treat different types of paediatric dystonia are outlined below.

Inherited dystonia without nervous system pathology

Systematic review evidence (n=111 patients)

Elkaim et al.[15] reported data for 111 patients who underwent DBS at a median age of 13 years (IQR 10–16). Of these, 102 had confirmed *DYT1* or *DYT6* mutations and nine were diagnosed with myoclonus-dystonia (seven of whom had DYT11 mutations). Bilateral GPi stimulation was performed in 107 patients. The BFMDRS-M and BFMDRS-D subscores improved by a median 77% (IQR 53%–94%) and 70% (IQR 43%–86%), respectively, with 93% of patients demonstrating some improvement and 88% having clinically significant improvement (≥20%) in BFMDRS-M subscores at a median follow up of 13.5 months.

Patients with DYT1 or DYT6 dystonia had a median improvement of 78% (IQR 54%-94%) in BFMDRS-M subscores and 70% (IQR 43%–86%) in BFMDRS-D subscores (median follow up 15 months), while those with myoclonus-dystonia had improvements of 68% (IQR 36%–85%) and 50% (IQR 15%–85%; mean follow up 10.5 months), in the two subscores respectively. All of the latter nine patients with myoclonus-dystonia had clinically significant improvement (≥20%): in five patients myoclonic movements improved by 83% on the Unified Myoclonus Rating Scale[29] (UMRS) action subscore and in one patient, the total score improved by 89%, compared with preoperative values.

Case series studies (n=21 patients)

Canaz et al.[37] reported on four patients with primary dystonia who received bilateral implants in the GPi at a median age of 12 years (range 5–16). Six months after surgery, the total BFMDRS scores had improved by a median 43% (range 30%–45%) and the Subjective Benefit Rating Scale[31i] was 1.75 (standard deviation [SD]

[i] Worse (-1), no benefit (0), minimal benefit (1), good benefit (2), excellent benefit (3)

0.5). However, the Subjective Benefit Rating Scale is highly affected by patient expectations and does not always correspond to the clinician's evaluation.[37]

Candela et al.[38] reported on six patients who underwent bilateral GPi DBS at a mean age of 12 years (range 7–16) for primary dystonia (n=4) or myoclonus-dystonia (n=2). Six months after surgery, the BFMDRS-M and BFMDRS-D subscores had improved by a mean 58% (SD 33.4%) and 41% (SD 29%), respectively, in the children with primary dystonia. For the two patients with myoclonus-dystonia, the improvements were 67% and 93% for the BFMDRS-M subscore and 40% and 100% for the BFMDRS-D subscore. Six months after surgery, improvements in myoclonic symptoms measured with the UMRS were 95% and 100% on the action subscore, and 50% and 75% on the function subscore. Postoperative quality of life outcomes measured with the Neuro-QOL scale[52] were inconsistent. Six months after surgery, there were some improvements in upper and lower limb function, stigma, social relationships and anger items, but scores for anxiety, fatigue, pain and cognitive function were worse, compared with baseline values, and there was no change in depression score.[38]

Tustin et al.[42] assessed 11 patients who received bilateral GPi DBS at a mean age of 12 years (range 7–19). Outcomes were measured using the Gross Motor Function Measure-88[53] (GMFM-88) and the BFMDRS, but the latter results were not extracted because they were previously reported by studies included in Elkaim et al.[15] The median improvement in gross motor function was statistically significant one year after surgery (p=0.02), but this was not maintained in the six patients with two-year follow-up data.

Case reports (n=2)

Oterdoom et al.[48] reported on the use of bilateral GPi DBS in a 9-year old patient with *DYT6* mutation. BFMDRS-M and BFMDRS-D subscores had improved by 46% and 3% over baseline values one year after surgery. After 15 months, the patient's condition deteriorated to status dystonicus, which required surgery to reposition the electrodes. There was no further recurrence of status dystonicus up to 24 months after the second surgery. By 3.4 years after the initial surgery, the BFMDRS-M and BFMDRS-D subscores had improved by 42% and 10%, compared with baseline values.

Jones et al.[47] used bilateral GPi DBS to treat a 15-year old patient with myoclonus-dystonia. Outcomes were measured with the Canadian Occupational Performance Measure[30], which captures a patient's perceived performance in everyday living. One year after treatment, the patient's perceived performance score had improved from 5.0 to 9.4 (parent rating 2.8 to 8.2) and the satisfaction score had improved from 2.6 to 9.6 (parent rating 2.2 to 8.8).

Inherited dystonia with nervous system pathology

Systematic review evidence (n=50)

Elkaim et al.[15] reported data for 50 patients with inherited dystonia and nervous system pathology who underwent DBS at a median age of 13.6 years (IQR 10 to 17). The BFMDRS-M subscores improved by a median 27% (IQR 3%–60%), but there was there was no overall change in BFMDRS-D subscores at a median follow up of 12 months. The subgroup of patients with pantothenate kinase-associated neurodegeneration (PKAN) (n=36) or Lesch-Nyhan syndrome (n=4) demonstrated clinically significant improvement (≥20%) in BFMDRS-M subscores (median 28% and 26%, respectively) at a mean 14.5 months after surgery, compared with baseline values. Patients with glutaric aciduria type 1 (n=5) had the worst response, with a median improvement in BFMDRS-M subscores of 6% at a median follow up of 12 months.

Case series and case reports (n=19)

Canaz et al.[37] reported on two patients, aged 7 and 17 years at the time of surgery, who received bilateral GPi DBS for dystonia related to PKAN and mitochondrial membrane protein-associated neurodegeneration.

Six months after surgery, the BFMDRS subscores had improved by 38% and 45%, and the Subjective Benefit Rating Scale scores were 2 and 3, respectively.

Canaz et al.[37] also reported on two patients, aged 14 and 16 years, with juvenile parkinsonism and focal dystonia who received bilateral STN DBS. Six months after surgery, the Hoehn and Yahr Scale[54] score had improved from 2.5 (mild symptoms) and 3 (balance impairment, mild to moderate disease) preoperatively to 1 (symptoms on one side only) for both patients. After surgery both patients scored 3 on the Subjective Benefit Rating Scale.

Tustin et al.[42] reported on 14 patients with various inherited dystonia aetiologies that were associated with nervous system pathology. After bilateral GPi DBS at a median age of 11 years (range 4 to 17), the median GMFM-88 score was relatively unchanged one year after treatment and was worse than the preoperative value by two years, although the latter change was not statistically significant.

Skogseid et al.[49] reported on a 12-year old patient with an *ACTB* gene mutation who underwent bilateral GPi DBS. Four years after surgery, the BFMDRS-M and BFMDRS-D subscores had improved by 66% and 44%, compared with preoperative values.

Acquired dystonia

Systematic review evidence (n=76)

Elkaim et al.[15] reported data for 76 patients (78% of whom had cerebral palsy) who underwent DBS at a median age of 12 years (IQR 8 to 17). Among the 59 children and adolescents with cerebral palsy, the BFMDRS-M and BFMDRS-D subscores improved by a median 11% (IQR 0%–21%) and 4% (IQR 0%–15%; median follow up 12 months). Patients with kernicterus (n=8) and stroke (n=3) also showed little improvement in BFMDRS-M subscores at a median follow-up of 12 months.

Case series and case reports (n=21)

Tustin et al.[42] reported on 20 patients, 19 of whom had cerebral palsy. Bilateral GPi DBS performed at a median age of 10.7 years (range 5.3 to 17.8) had minimal effect on GMFM-88 scores at either the one- or two-year follow-up.

Canaz et al.[37] reported on one patient with cerebral palsy who received bilateral GPi DBS at 8 years of age. Six months after surgery, the child's BFMDRS score had improved by 41% and the Subjective Benefit Rating Scale score was 1.

Idiopathic dystonia

Systematic review evidence (n=72)

Elkaim et al.[15] reported data for 72 patients who underwent DBS at a median age of 13.5 years (IQR 10 to 17). BFMDRS-M and BFMDRS-D scores improved by a median 51% (IQR 24%-73%) and 39% (IQR 20%-59%) at a median follow up of 20 months. Clinically significant improvement (≥20%) in BFMDRS-M scores was observed in 80% of patients.

Case series and case reports (n=15)

Tustin et al.[42] reported results for 15 patients who received bilateral DBS at a median age of 12 years (range 7-19). Improvements in gross motor function were almost statistically significant at the one-year follow up, but this was not maintained at the two-year follow up.

Status dystonicus

Systematic review evidence (n=18)

Elkaim et al.[15] reported data for 18 patients receiving DBS for status dystonicus: six had DYT1 dystonia, five had idiopathic dystonia, three had PKAN dystonia, two had Batten disease and two had idiopathic dystonia. The dystonic crisis was resolved in 89% of the 18 patients. The BFMDRS-M subscores had improved a median 54% (IQR 18%-89%) at last follow-up (median 11 months), and six patients had achieved over 85% improvement, compared with preoperative values.

Case series and case reports (n=18)

Effectiveness data from the case series studies and case reports are provided in Table 3.

Koy et al.[40] documented outcomes for five patients with *GNAO1* mutation-induced status dystonicus (duration not stated) who received GPi DBS at a mean age of 11.5 years (range 6–15; n=4 patients). The crisis was resolved in all patients (time not stated), and four of the five patients had no relapses (longest follow-up 10 years). One patient experienced multiple recurrences due to dysfunction of the DBS system. Preoperative and postoperative BFMRDS-M and BFMRDS-D scores were reported for three patients; these improved by a mean of 29% and 15%, respectively.

Benato et al.[36] reported on four children (two with methylmalonic acidemia and two with *GNA01* mutation) who were treated with DBS for status dystonicus (mean duration 2.3 months) at a mean age of 9 years. The STN was targeted in one patient and the GPi was targeted in the other three. Status dystonicus was resolved in all cases within a mean 14 days, with no recurrence in four patients over the mean five-year follow-up period. The modified Rankin Scale score[55] improved from 5 (severe disability, requires constant care) to 4 (moderately severe disability, requires assistance for bodily needs) in all patients after surgery. One patient experienced two more episodes of dystonic storm due to electrode displacement, which was resolved with additional surgery.

Waak et al.[43] reported on three children with *GNAO1* mutation and cerebral palsy who received bilateral GPi DBS for status dystonicus (duration not reported). Dystonic storm was resolved one to six weeks after surgery, with no relapse occurring by the last follow up (range 12–26 months).

Canaz et al.[37] reported on two patients, one with primary dystonia and the other with PKAN, who received GPi DBS for status dystonicus (duration not reported) at the ages of 5 and 7 years. Dystonic storm was resolved in both patients, with no relapses up to six months after surgery, and the BFMRDS score improved by a mean 40%.

Lobato-Polo et al.[41] reported on two patients aged 8 and 10 years of age with dyskinetic cerebral palsy who underwent bilateral GPi DBS for status dystonicus (mean duration 5.5 days). Resolution of dystonic storm was achieved 7 and 21 days after surgery, with no relapse occurring in the following 46 and 49 months respectively. Improvement in the BFMRDS-M and Unified Dystonia Rating Scale[54] scores ranged from 60% to 61% and from 51% to 79%, respectively, at last follow up (range 46 to 49 months).

Barbosa et al.[45] reported on a 13-year old patient with *DYT1* mutation who underwent bilateral STN DBS for refractory status dystonicus (three months' duration). The crisis was resolved in 14 days and two months after surgery, the BFMDRS-M score had improved by 57% compared with the preoperative value. There were no relapses up to 10 months after surgery.

Table 3: Effectiveness data from primary studies on DBS for paediatric status dystonicus

Study	Diagnosis	*N*	Follow-up	Rate of SDy resolution (%)	Time to resolution	Recurrence rate (%)
Barbosa et al. [45]	*DYT1* mutation	1	10 months	100%	2 weeks	0%
Benato et al.[36]	Methylmalonic acidemia (n=2) *GNAO1* mutation (n=2)	4	Mean 5 years	100%	Mean 14 days	25%[a]
Canaz et al.[37]	Primary dystonia PKAN	2	6 months	100%	2 weeks (n=1) Not stated (n=1)	0%
Honey et al. [46]	*GNAO1* mutation	1	6 months	100%	10 days	0%
Koy et al.[40]	*GNAO1* mutation	5	Longest follow-up 10 years	100%	Not stated	20%[b]
Lobato-Polo et al.[41]	Cerebral palsy	2	27 months	100%	Range 7–21 days	0%
Waak et al[43]	Cerebral palsy and *GNAO1* mutation	3	12–26 months	100%	1–6 weeks (n=2)	0%

N: total number of patients; PKAN: pantothenate kinase-associated neurodegeneration; SDy: status dystonicus
[a]Due to dislocation of left electrode; no further recurrences after revision surgery
[b]Loss of benefit due to dysfunction of DBS system requiring several lead replacements

Honey et al.[46] treated a 10-year old patient with bilateral GPi DBS for *GNAO1* mutation–induced status dystonicus (two months' duration). The crisis was resolved 10 days after surgery and no relapses occurred in the six-month follow-up period. Scores on the Paediatric Barry-Albright Dystonia Scale and Caregiver Priorities and Child Health Index of Life with Disabilities[56] scale improved by 81% and 58%, respectively, compared with preoperative values.

Predictors of outcome

Elkaim et al.[15] conducted univariate (301 patients) and multivariable (77 patients from 38 studies) hierarchical mixed-effects analyses to identify predictors of outcome. Patient factors associated with better outcome included a diagnosis of idiopathic dystonia or inherited dystonia without nervous system pathology; older age at dystonia onset; and truncal involvement ($p<0.05$). Age and severity of dystonia at surgery were not associated with treatment response. Compared with the best responders, children and adolescents with inherited dystonia with nervous system pathology had comparatively lower, but still clinically significant, improvement, whereas patients with acquired dystonia did not generally benefit from DBS.

Koy et al.[39] grouped outcome data for 42 patients by dystonia aetiology as shown in Table 4. Since these data could not be disaggregated, they are reported separately from the data in the preceding sections. The majority of the patients received bilateral GPi DBS. The findings suggest that patients with acquired dystonia benefited the least from treatment, which is in agreement with the findings in the Elkaim et al. analyses.

Table 4: BFMDRS data from Koy et al.[39] by dystonia type (mean follow up 4.6 years, range 1 month to 15 years)

Diagnosis	*N*	Preoperative score	Postoperative score	*p*-value
Isolated inherited and idiopathic dystonia	9	Mean 57.4 (SD 23.4)	Mean 27.6 (SD 16.3)	<0.05
Combined inherited and idiopathic dystonia	22	Mean 67.7 (SD 33.6)	Mean 56.2 (SD 36.3)	<0.05
Acquired dystonia	11	Mean 71.0 (SD 28.3)	Mean 59.9 (SD 30.7)	Not statistically significant
Combined groups	**42**	**Mean 65.9 (SD 30.2)**	**Mean 52.1 (SD 33.8)**	**<0.05**

BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; *N*: total number of patients; SD: standard deviation.

Question 2b: Safety of DBS for the various types of paediatric dystonia

Thirty-five studies (level IV evidence) reported safety outcomes: 24 cited by Elkaim et al.[15] (n=260 patients) and 11 studies published after Elkaim et al.[15] (n=159 patients). Data extracted from 34 of the studies are tabulated in Appendix 5. An additional recently published study combined data from 10 DBS centres across Germany and Vienna (n=72 patients).[39] These data are reported separately at the end of this section.

For the majority of the 34 studies, it was not possible to disaggregate the data according to dystonia type in any meaningful way. Safety outcomes were often reported anecdotally and without reference to the time after surgery when they occurred, which hindered data pooling. Nonetheless, these data can be useful for noting overall trends.

Among the studies that specifically mentioned complications in the early postoperative period (≤1 month after surgery), hardware-related problems were the most commonly reported problem. Many studies did not report the time after surgery when these malfunctions occurred, but in the few studies that did, these complications usually happened at least six months after the surgery. Overall, electrode migration, dislodgement or fracture occurred in 17% of 212 patients, all of whom required revision surgery to rectify the problem. Recharger malfunction requiring replacement occurred in 30% of 168 patients, with pulse generators unexpectedly switching off in 6% of 174 patients. Unspecified technical malfunctions occurred in a further 7% of 184 patients.

Surgical site infections or seromas (a collection of fluid that builds up under the surface of the skin) were the next most commonly reported adverse events, occurring in 9% (16/170) of patients within the first month of surgery. Device removal was required in 30% of these 16 patients. These complications continued to be the most commonly reported from one to six months after surgery, with surgical site infection or skin erosion occurring in 14% (20/145) of patients; partial or complete device removal was required in 85% of these 20 patients. The overall rate of surgical site infection, irrespective of time after surgery, was 12% (48/412); partial or complete device removal was required in 63% of the 48 patients. Stimulation-induced side effects, such as hemiparesis, dyskinesia or slurred speech, were rare and generally mild or transient, occurring in 4% of 215 patients. Only two of these patients found the side effects intolerable.

Koy et al.[39] reported data from 72 patients categorised according to dystonia aetiology, with a mean postoperative follow up of 4.6 years (1 month to 15 years). None of the patients experienced intraoperative complications, and those occurring in the immediate postoperative period (≤1 month) were transient. The most commonly reported complication during this period was cerebrospinal fluid collection around the surgical site, which occurred in 10% of patients. Patients who received the electrode and impulse generator implants in a single surgery (n=16) were more likely to experience adverse events during the first six months

than those who underwent two-stage surgery (n=14, $p<0.05$), although none of these complications were infections. At least one surgical intervention was required in 13% (9/72) of patients for a wound infection and in 26% (19/72) of patients for hardware problems. In line with the other studies, hardware-related problems were the most common cause of complications at least one month after surgery. Most adverse events occurred beyond the six-month follow-up period: 20% in the first six months and 56% thereafter (n=55 patients with at least two years' follow-up).

The total risk of a complication requiring surgical intervention was 8% per electrode-year (95% confidence interval [CI] 5.9%–10.3%). The risk of experiencing a wound-related complication requiring surgical intervention was 2% (95% CI 1.2%–3.6%), while the risk of an irreversible hardware-related event was 6% per electrode-year (95% CI 4.1%–7.9%). The rates of adverse events did not differ according to dystonia aetiology. However, there was a tendency for higher rates of complications beyond the six-month postoperative period in patients aged seven to nine years of age, and in those with more severe dystonia at surgery.

Question 3: International service delivery models and funding mechanisms for paediatric DBS

A single relevant evidence-based clinical practice guideline[51] was identified, but it was published in 2011 and its recommendations were based on literature published up to September 2009 (Table 5). Since the median life span of a clinical practice guideline is five years from publication, this guideline is considerably outdated.[57, 58] However, it was the only guideline identified that specifically mentioned the use of DBS in paediatric patients with dystonia, stating that age should not be a criterion for withholding GPi DBS. It did not provide any information on service delivery models for paediatric DBS.

Table 5: Summary of recommendations from the included clinical practice guideline

Guideline details	Recommendations	Evidence gaps noted in the guideline
Bronte-Stewart et al.[51] Multinational **Financial support:** Not stated **Population:** Patients with dystonia **Intended Users:** Not stated	Age itself should not be used as an inclusion or exclusion criterion for GPi DBS: **children as well as adults can benefit from the procedure**. Any patient with a progressive generalised dystonia should consider surgery before developing fixed skeletal deformities. GPi DBS should be considered for patients with progressive generalised dystonia who do not respond adequately to medical therapy and who are limited in their activities of daily living. For dystonic syndromes secondary to other causes, DBS might be considered in cases of tardive dystonia, hyperkinetic cerebral palsy, and/or cases with severe disability, although more large prospective trials are needed to support evidence of benefit. Secondary dystonia from encephalitis and/or structural lesions may not respond well to DBS. Testing for DYT1 dystonia or myoclonus-dystonia (DYT11) is helpful to confirm the diagnosis and for counselling patients regarding outcomes of treatment.	More evidence is needed on: • The relative contribution of age and symptom duration on surgical outcomes • Which clinical features are predictive of response to DBS • Outcomes related to disability, quality of life and non-motor symptoms • The efficacy of DBS in other genetic dystonias and secondary dystonia syndromes • Whether surgical outcomes differ by mutation status

Gaps in the evidence

There was a dearth of evidence for Questions 1 and 3. The absence of comparative studies meant that there was no evidence available to answer research Question 1. Since DBS is currently considered a last resort treatment reserved for children who have not responded to best supportive care, the latter may not be an appropriate comparator for DBS. Unless the status of DBS in the care pathway changes, it is unlikely that studies comparing DBS with best supportive care for paediatric dystonia will be forthcoming, particularly given the small number of patients involved and the highly specialised nature of the treatment. Aside from a single, outdated clinical practice guideline, there was a similar lack of information available to inform research Question 3.

For research Question 2, the evidence base comprised small- to moderate-sized case series studies and numerous, sometimes poorly-reported, case reports. The NHMRC evidence matrix for Question 2 is shown in Table 6. While the quality of the recently published case series studies was relatively high, they nonetheless suffered from the limitations inherent in retrospectively collected data. In addition, inclusion of case reports and small case series studies, while necessary, may skew the results; patients who have good outcomes are more likely to be reported than those who do not. The studies were often heterogeneous with respect to study populations and the scales used to measure treatment effectiveness, which in the latter case hampered synthesis of the data. However, the majority of the studies reported outcome data in a manner that allowed disaggregation of results for the various dystonia aetiologies.

Table 6: NHMRC body of evidence matrix for research Question 2

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base[a]	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Populations studied in body of evidence are the same as the target population	Populations studied in the body of evidence are similar to the target population	Populations studied in body of evidence differ from target population but it is clinically sensible to apply this evidence to target population	Populations studied in body of evidence differ from target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

[a]Level of evidence determined from the NHMRC evidence hierarchy[34, 35]

Limitations

This rapid review had some limitations. Only English-language studies were eligible for inclusion, and article screening, study selection, data extraction and quality appraisal were conducted by a single reviewer. Study authors were not contacted to obtain additional information. Also, the systematic review by Elkaim et al.[15] comprised a substantial portion of the evidence base, which means that this Evidence Check shares that review's limitations. For example, Elkaim et al.[15] included only studies that measured preoperative and postoperative outcomes with either the BFMDRS or the Barry-Albright Dystonia Scale. Other outcome measures, such as pain and function, were not included because they were often sporadically or inadequately reported. While this was a valid rationale, it means that this Evidence Check, like the systematic review, may have missed data on other outcomes such as pain and psychological wellbeing. However, after reviewing full-text versions of a substantial number of the studies excluded by Elkaim et al.[15], and given the fact that the International Classification of Functioning, Disability and Health[59] is rarely used to evaluate DBS[15], it is unlikely that any significant data were omitted. In addition, the criteria used by this Evidence Check to select studies published after Elkaim et al.[15] were expansive, which ensured that any data on alternate outcomes were captured.

Discussion

This Evidence Check rapid review examined the evidence for using DBS to treat children and adolescents with dystonia. The evidence base comprised data on effectiveness outcomes for 457 patients and safety outcomes for 491 patients. Despite the limitations inherent in the mostly retrospective, level IV evidence base, certain trends were evident.

Effectiveness

DBS targeted to the GPi provided significant improvement in BFMDRS scores for children and adolescents with inherited dystonia without nervous system pathology, particularly those with *DYT1*-associated dystonia. There was some suggestion that quality of life may also be improved, but the different measurement tools used and sporadic reporting of these outcomes hindered more definitive conclusions. The small number of patients with myoclonus-dystonia who received DBS also achieved significant improvements in both dystonia and myoclonus symptoms. Children and adolescents with idiopathic dystonia benefited from GPi DBS, with 80% of patients achieving significant improvements in BFMDRS scores. DBS was also an effective treatment for life-threatening status dystonicus, although the number of patients studied was small. Other factors associated with a good response to DBS included older age at dystonia onset and truncal involvement, whereas neither age nor severity of dystonia at surgery was associated with a treatment response.

In contrast, the outcomes for patients with inherited dystonia accompanied by nervous system pathology were more variable and generally inferior, but still clinically significant. Within this dystonia subtype, the BFMDRS scores were most improved in patients with PKAN or Lesch-Nyhan syndrome. The significant improvement in motor score observed in a patient with an *ACTB* gene mutation suggests that other as yet unidentified aetiological subgroups within this dystonia subtype may also derive benefit from DBS.

GPi DBS generally had minimal effect on BFMDRS scores in children and adolescents with acquired dystonia, particularly in those with dyskinetic cerebral palsy. This was also the case for patients with dystonia due to kernicterus or stroke, although the number of patients studied was very small.

Safety

While DBS is completely reversible, it is not without hazards. The procedure itself was relatively safe, but surgical site infections and seromas occurred in 10% of patients within a month of surgery, with re-intervention being required in nearly one-third of these cases. Hardware-related adverse events requiring repeat surgery occurred in 17% to 26% of patients, usually at least six months after surgery. Recharger malfunctions requiring replacement occurred in nearly a third of patients. However, stimulation-induced side effects were rare, occurring in only 4% of patients. The total risk of a complication requiring surgical intervention was 8% per electrode-year, and complication rates were similar across the various dystonia subtypes. Children aged seven to nine years of age and those with more severe dystonia at surgery tended to have a higher risk of complications than other patients.

Complication rates after DBS surgery are generally higher among children and adolescents than adults.[12] Since DBS is a last resort treatment in paediatric patients, they have often spent a greater proportion of their lives with severe dystonic symptoms.[12, 18] The secondary complications associated with severe long-term dystonia, such as sleep disturbances and feeding problems, can lead to low immunity and malnutrition, which complicate postoperative recovery. In addition, children are more likely to experience hardware-related problems, such as electrode dislocation and tight lead extensions, because of the changes in brain volume, head circumference and body size that occur as they grow.[12, 18, 37, 38]

Cost and access considerations

While there was no information available on the cost-effectiveness of administering DBS to paediatric patients with dystonia, Akano et al.[60] noted that the average cost of hospitalisation in the United States (US) for paediatric patients (mean age 14.5 years) undergoing DBS for various indications was approximately $USD43,900 ($AUD63,500). Although this figure is not directly applicable to the Australian healthcare context, it nonetheless highlights the significant resources required for this highly specialised treatment. Additionally, close follow-up by an experienced team is essential for successful long-term maintenance of DBS. This requires ongoing return visits, which may be difficult for patients who live far from experienced providers.[17]

Most dystonic patients have lifelong care needs, which often start at a young age. An economic analysis by Yianni et al.[61], which used data from 26 patients undergoing DBS for dystonia (age not specified), estimated that 63% of the total costs of DBS over a period of two years from the initial procedure were attributed to preoperative and surgical costs, with only 37% contributed by follow-up management and complications. While DBS is an expensive treatment, the upfront cost will likely be offset by the savings from reduced medication use, fewer hospitalisations, decreased nursing care needs, improved quality of life, increased participation in school and employment and decreased burden on family members and other caregivers.

Knowledge gaps

Although the evidence for DBS in paediatric primary dystonia is promising, many questions remain. Data are sparse for patients with secondary dystonia and its numerous aetiologies. The effects of high-frequency neuromodulation on a maturing brain are not yet known, although there is limited evidence from a small study indicating that cognition may not be adversely affected.[12, 62] One qualitative study[63] has shown that this may be an important consideration for parents of children who are less physically and cognitively impaired because there is more to lose if the surgery does cause unintended harms. It is also unclear how DBS affects pain, mood, quality of life and overall health status, and whether there is an optimal implant site for each dystonia subtype.[17, 18] The economic impact of a treatment begun in childhood that requires lifelong maintenance and follow-up also needs to be assessed.[64]

Considerations for future research

Adequately assessing the effectiveness of DBS in children and adolescents is challenging. Although the BFMDRS is the most commonly used measure of dystonia impairment, it is often criticised for not discriminating between postures and movements caused by non-dystonic symptoms. Also, its accuracy for measuring outcomes in children may not be ideal since it was originally designed for use in adults. Other commonly reported scales such as the Barry-Albright Dystonia Scale and the UMRS either do not capture more subjective factors such as wellbeing, quality of life and disease burden,[3, 65] or may not be sensitive enough to detect subtle improvements in pain and function that could be significant to patients.[12, 66]

Parents of children disabled by secondary dystonia make decisions about DBS surgery based on expectations of potential improvements in physical and functional domains as well as quality of life (e.g. pain relief)[63], but these aspects are rarely reported even though moderate to severe pain is experienced by a quarter of patients with secondary childhood dystonia.[20, 66, 67] Future studies should include severity scales and measures of quality of life, autonomy and pain in accordance with the International Classification of Functioning, Disability and Health.[3, 59, 68] It is also important that studies have an adequate follow-up period, particularly since the effects of DBS may be cumulative and could take at least a year to stabilise in certain patient groups.[12, 69]

Ongoing and recently completed clinical trials listed in the US National Library of Medicine database ClinicalTrials.gov have compared DBS with sham, placebo or neuroablative treatment, or assessed technical aspects such as different brain targets or devices, in patients with paediatric dystonia. In addition, the recent

establishment of two synchronised, prospective multicentre registries for paediatric DBS in Germany (GEPESTIM) and the United States (the Pediatric International DBS Registry Project) should help answer some of the outstanding questions relating to the use of DBS in paediatric patients with dystonia. As a case in point, data on 72 patients from GEPESTIM were included in this Evidence Check.[39]

Conclusion

Question 1: Safety, effectiveness and cost effectiveness of DBS compared with best supportive care

No studies were identified that compared DBS with best supportive care in paediatric patients with dystonia. Given the direction of current research efforts and the fact that DBS is considered a last resort in this patient group, it is unlikely that trials comparing these two interventions will be forthcoming.

Question 2a: Effectiveness of DBS for the various types of paediatric dystonia

Generally consistent results from low-level evidence suggested the following:

- The paediatric patients who respond best to DBS in terms of improved motor function are those with idiopathic dystonia or inherited dystonia without nervous system pathology
- Patients with inherited dystonia and nervous system pathology who undergo DBS have comparatively lower, but still clinically significant, improvement in motor function, with most improvement seen in patients with PKAN or Lesch-Nyhan syndrome
- DBS is largely ineffective in improving motor function in patients with acquired dystonia, particularly those with dyskinetic cerebral palsy
- DBS may be an effective treatment for halting life-threatening status dystonicus, although the number of patients studied was small
- Other factors associated with a good response to DBS include older age at dystonia onset and truncal involvement
- Age and severity of dystonia at surgery do not appear to affect treatment response
- It is unclear whether improvements in motor function translate to better quality of life and overall health status.

Question 2a: Safety of DBS for the various types of paediatric dystonia

Generally consistent results from low-level evidence suggested the following:

- The DBS implantation procedure is relatively safe, although patients who have the electrode and impulse generator implanted in the same surgical session are more likely to experience a complication in the first six months than those who have two-stage surgery
- The total risk of a complication requiring surgical intervention is 8% per electrode-year. The most common complications that require additional surgery are hardware-related adverse events (range 17%–26%) and surgical site infections (range 7%–13%), which generally occur at least six months after the initial surgery
- Stimulation-induced side effects are rare, occurring in only 4% of patients
- The rates of adverse events do not differ among the dystonia subtypes
- Complications are more likely to occur in children aged seven to nine years of age compared with other age groups, and among those with more severe dystonia.

Question 3: International service delivery models and funding mechanisms for paediatric DBS

Aside from a single outdated clinical practice guideline that made passing mention of the use of DBS in paediatric patients with dystonia, no information was identified on service delivery models or funding mechanisms for paediatric DBS.

The bottom line

DBS has been used in children and adolescents with medically refractory idiopathic dystonia and inherited dystonia without nervous system pathology for more than a decade, despite the lack of evidence-based guidelines supporting its use in these patients. The growing body of level IV evidence considered in this rapid review generally supported the use of DBS for improving motor function and disability, although more data need to be collected on other aspects of patient wellbeing such as quality of life, cognitive function, pain and autonomy. Patients with medically refractory inherited dystonia with nervous system pathology may also benefit from DBS, but it is not yet clear which aetiologies within this subgroup would achieve the most improvement. DBS should be considered as an option for the emergency treatment of paediatric patients experiencing medially refractory, life-threatening status dystonicus.

While DBS is generally well tolerated, it is associated with complications that may require further surgery, and it requires ongoing, lifelong maintenance and follow-up from specialised providers. Data from two recently established prospective multicentre registries will help bridge the current knowledge gaps on the use of DBS in children and adolescents with dystonia.

Appendix 1: Literature search strategy

Database[a]	Search terms	
PubMed	1	Exp "Child" (Subject Heading)
	2	Exp "Child Health" (Subject Heading)
	3	Child (All Fields)
	4	Children (All Fields)
	5	Child health (All Fields)
	6	Exp "Pediatrics" (Subject Heading)
	7	Pediatrics (All Fields)
	8	Paediatrics (All Fields)
	9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
	10	Exp "Dystonia" (Subject Heading)
	11	Exp "Torsion Dystonia" (Subject Heading)
	12	Dystonia (All Fields)
	13	Segawa syndrome (All Fields)
	14	10 OR 11 OR 12 OR 13
	15	Exp "Brain Depth Stimulation" (Subject Heading)
	16	Exp "Electrotherapy" (Subject Heading)
	17	Deep brain stimulation (All Fields)
	18	Deep brain stimulations (All Fields)
	19	Brain stimulation, deep (All Fields)
	20	Brain stimulations, deep (All Fields)
	21	"Electrical stimulation of the brain" (All Fields)
	22	Stimulation, deep brain (All Fields)
	23	Stimulations, deep brain (All Fields)
	24	OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
	25	Electrical (All Fields)
	26	Electric (All Fields)
	27	Electrode* (All Fields)
	28	25 OR 26 OR 27
	29	Stimulation (All Fields)
	30	Brain (All Fields)
	31	(28 AND 29) AND 30
	32	24 OR 31
	33	9 AND 14 AND 32

Database[a]	Search terms
Embase	1 Child (MeSH Term)
	2 Child Health (MeSH Term)
	3 Child (All Fields)
	4 Children (All Fields)
	5 Child health (All Fields)
	6 Pediatrics (MeSH Term)
	7 Pediatrics (All Fields)
	8 Paediatrics (All Fields)
	9 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
	10 Dystonia (MeSH Term)
	11 Dystonia Musculorum Deformans (MeSH Term)
	12 Dystonia (All Fields)
	13 Segawa syndrome (All Fields)
	14 10 OR 11 OR 12 OR 13
	15 Deep brain stimulation (MeSH Term)
	16 Electric Stimulation Therapy (MeSH Term)
	17 Deep brain stimulation (all fields)
	18 Deep brain stimulations (All Fields)
	19 Brain stimulation, deep (All Fields)
	20 Brain stimulations, deep (All Fields)
	21 "Electrical stimulation of the brain" (All Fields)
	22 Stimulation, deep brain (All Fields)
	23 Stimulations, deep brain (All Fields)
	24 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
	25 Electrical (All Fields)
	26 Electric (All Fields)
	27 Electrode* (All Fields)
	28 25 OR 26 OR 27
	29 Stimulation (All Fields)
	30 Brain (All Fields)
	31 (28 AND 29) AND 30
	32 24 OR 31
	33 9 AND 14 AND 32
The Cochrane Library (Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects - Health Technology Assessment)	Dystonia; "deep brain stimulation"
Guideline agencies/repositories	
Australian Clinical Practice Guidelines Portal	Dystonia; "deep brain stimulation"
Canadian Medical Association Clinical Practice Guideline Infobase	Dystonia; "deep brain stimulation"

Database[a]	Search terms
Guidelines International Network (G-I-N)	Dystonia; "deep brain stimulation"
National Guidelines Clearinghouse (NGC) – until July 16, 2018	Dystonia; "deep brain stimulation"
National Institute for Health and Care Excellence (NICE)	Dystonia; "deep brain stimulation"
Scottish Intercollegiate Guidelines Network (SIGN)	Dystonia; "deep brain stimulation"
HTA and coverage agencies	
Agency for Healthcare Research and Quality (AHRQ)	Dystonia; "deep brain stimulation"
Aetna Clinical Policy Bulletins	Dystonia; "deep brain stimulation"
BlueCross BlueShield Technology Assessments	Dystonia; "deep brain stimulation"
Canadian Agency for Drugs and Technologies in Health (CADTH)	Dystonia; "deep brain stimulation"
Institute for Clinical Evaluative Services (ICES)	Dystonia; "deep brain stimulation"
Ontario Health Technology Advisory Committee (OHTAC)	Dystonia; "deep brain stimulation"
National Institute for Health Research (NIHR) Health Technology Assessment	Dystonia; "deep brain stimulation"
Relevant professional societies	
American Association of Neurological Surgeons	Dystonia; "deep brain stimulation"
European Academy of Neurology	Dystonia; "deep brain stimulation"
Grey literature	
Google	Dystonia; "deep brain stimulation"
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	Dystonia; "deep brain stimulation"

[a]Literature search was conducted on 12 June 2019

Note: "*" is a truncation character that retrieves all possible suffix variations of the root word, e.g., Surg* retrieves surgery, surgical, surgeon, etc.

Searches separated by semicolons were entered separately into the search interface

Appendix 2: Included studies

Table 2.1: Included systematic review characteristics and data summary

Review	Study Population	Comparison/Outcome/ Intervention Details	Relevant Results/Authors' Conclusions
Elkaim et al.[15] Canada **Objective:** To evaluate the efficacy of DBS across dystonia subtypes in children and identify patient phenotypes associated with treatment response **Studies Reviewed:** 72 case series and case reports **Financial support:** No funding received; no conflicts of interest **Methodological quality:** High (completely fulfilled 13/15 applicable criteria)	**Included Patients:** Total number: *Status dystonicus*: n=18 *Dystonia*: n=321 Inherited dystonia without degeneration:n=111: *DYT1* or *DYT6* mutations (n=102); myoclonus-dystonia (n=9) Inherited dystonia with degeneration (n=50) Acquired dystonia with static lesions (n=76) Idiopathic dystonia (n=72) Other (diagnoses not generally recognised as having an etiological link to dystonia) (n=12) Condition: Dystonia or status dystonicus Age: ≤21 years of age **Exclusion Criteria:**	**Intervention:** DBS *Target*: Globus pallidus interna (GPi) (n=309); STN only (n=3); STN + GPi (n=3); thalamus ± GPi (n=3); pedunculopontine nucleus + GPi (n=1); internal capsule (n=1); not stated in review (n=1) **Comparisons:** Not applicable; only case series/reports available for review **Outcomes:** Changes in the Burke-Fahn-Marsden or Barry-Albright rating scale, complications	**Overall BFMDRS:** *Motor subscore (n=312, median FU 12 months):* Median improvement: 42% (IQR 12%–80%); 86% showed improvement Clinically significant (≥20%) improvement: 66% *Disability subscore (n=218)*: Median improvement: 28% **Inherited dystonia without degeneration (n=111, median FU 13.5 months) - BFMDRS:** Median improvement: 77% (IQR 53% to 94%) (motor subscore); 70% (IQR 43% to 86%) (disability subscore) Clinically significant (≥20%) improvement: 88% *Subgroups*: DYT1/DYT6 dystonia (n=102): median improvement 78% (IQR 54% to 94%) (motor); 70% (IQR 43% to 86%) (disability) (median FU 15 months) Myoclonus-dystonia (n=9): median improvement 68% (median FU 10.5 months) **Inherited dystonia with degeneration (n=50, median FU 12 months) - BFMDRS:**

	Studies published prior to January 1999; studies without individual patient data; studies not reporting outcomes using the Burke-Fahn-Marsden[28]Dystonia Rating Scale (BFMDRS) or Barry-Albright[27] Dystonia Scale; data on children with dystonia parkinsonism		Median improvement: 27% (motor); 0% (disability) *Subgroups*: PKAN dystonia (n=36): median improvement 28% (motor) Glutaric aciduria type 1 (n=5): median improvement: 6% (motor) Lesch-Nyhan syndrome (n=4): mean improvement: 26% (motor) (mean FU 14.5 months) **Acquired dystonia – BFMDRS (n=76, median FU 12 months):** Cerebral palsy (n=59): median improvement 11% (motor); 4% (disability) Kernicterus (n=8): median improvement 11% (motor); 4% (disability) Stroke (n=3): mean improvement 11% (motor) (mean FU 12 months) **Idiopathic dystonia (n=72, median FU 20 months) - BFMDRS:** Median improvement: 51% (motor); 39% (disability) Clinically significant (≥20%) improvement: 80% **Status dystonicus (n=18, median FU 11 months) - BFMDRS:** Median improvement: 54% (IQR 18% to 89%) (motor) Crisis resolution (n=18): 89% **Responders to DBS:** • Best responders: idiopathic dystonia or patients with inherited dystonia without degeneration ($p<0.05$) • Worst responders: acquired dystonia • Patients with inherited dystonia with nervous system pathology had comparatively lower, but still clinically significant, improvement • Other factors associated with better outcome: older age at dystonia onset and truncal involvement ($p<0.05$) **Safety:**

			The most commonly reported complications were infections and mechanical failure. **Authors' conclusion:** The data suggest that DBS is effective and should be considered in selected children with inherited or idiopathic dystonia. Patients with DYT1 dystonia tend to have better outcomes, but patients with idiopathic dystonia also respond well. Although less effective in other types of dystonia, DBS may be considered because of the high number of medically refractory patients. DBS should be considered as an emergency treatment for status dystonicus.

DBS: deep brain stimulation; FU: follow up; IQR: interquartile range; GPi: Globus pallidus interna; STN: Subthalamic nucleus

Table 2.2: Included primary study characteristics

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
Case Series						
Canaz et al.[37] Turkey Level IV evidence (retrospective) Methodological quality: 13/19 criteria fulfilled (1 not applicable) Length of FU: 6 months Losses to FU: 0%	**Primary, secondary or heredodegenerative dystonia or levodopa-responsive juvenile parkinsonism refractory to medication (total n=9)** Subtypes: *Primary dystonia*: n=4 (male) Age at onset: mean 5.8 years (range 3–9 years) Duration of symptoms: mean 5.5 years Age at surgery: mean 11.3 years (range 5–16 years) *Juvenile parkinsonism*: n=2 (female) Age at onset: 11 and 14 years Duration of symptoms: mean 2.5 years Age at surgery: 14 and 16 years *Cerebral palsy*: n=1 (female) Age at onset: 0 years Duration of symptoms: 8 years Age at surgery: 8 years *MPAN dystonia*: n=1 (female) Age at onset: 9 years Duration of symptoms: 8 years Age at surgery: 17 years *PKAN dystonia*: n=1 (female) Age at onset: 5 years	Bilateral GPi DBS (n=7) Bilateral STN DBS (n=2 patients with juvenile parkinsonism) Pulse generator battery type: Not reported Pulse generator location: Chest or upper abdomen depending on patient size	✓	✓		None to declare

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
	Duration of symptoms: 2 years Age at surgery: 7 years *Note*: Two patients from this study also had status dystonicus; data pertaining to that condition were extracted separately					
Candela et al.[38] Spain Level IV evidence (prospective) Methodological quality: 13/19 criteria fulfilled (1 not applicable) Length of FU: 6 months Losses to FU: 0%	**Isolated or combined dystonia refractory to medication (total n=6)** Age at onset: mean 5 years (range 2.5–10) Duration of symptoms: mean 7 years (range 0.5–12) Age at surgery: mean 11.8 years (range 7–16) Subtypes: *Myoclonus dystonia*: n=2 (female) *Primary dystonia*: n=3 (2 female) *Choreo-dystonia*: n=1 (male)	Bilateral GPi DBS Pulse generator battery type: Rechargeable Pulse generator location: Abdomen	✓	✓	✓	1 of 10 co-authors has received honoraria and financial support for research from Medtronic
Koy et al.[39] Austria and Germany Level IV evidence (retrospective) Methodological quality: 14/19 criteria fulfilled	**Dystonia (total n=72; 46 male)** Age at onset (n=61): mean 4.4 years (SD 3.5) Duration of symptoms: not stated Age at first surgery: mean 12.3 years (SD 3.4; range 4-18)	Bilateral GPi DBS (n=62) Unilateral or bilateral STN DBS (n=2) Other targets (n=8)	✓	✓		4 of 27 authors received honoraria or educational support from Medtronic

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
Length of FU: mean 4.6 years (SD 4 years; range 1 month–15 years) Losses to FU: 42% had missing efficacy data	<u>Subtypes</u>: *Isolated inherited and idiopathic*: n=16 (11 male) Age at onset: mean 6.6 years (SD 2.3)[b] Duration of symptoms: not stated Age at surgery: mean 12.1 years (SD 3.3) *Combined inherited and idiopathic*: n=34 (21 male) Age at onset: mean 4.7 years (SD 3.4)[b] Duration of symptoms: not stated Age at surgery: mean 12.3 years (SD 3.3) *Acquired*: n=22 (14 male) Age at onset: mean 2.6 years (SD 3.5)[b] Duration of symptoms: not stated Age at surgery: mean 12.6 years (SD 3.7)	<u>Pulse generator battery type</u>: Rechargeable: 39% Non-rechargeable: 49% Unknown: 12% <u>Pulse generator location</u>: Below the clavicle or in the abdomen				
Tustin et al.[42] United Kingdom (UK) Level IV evidence (mixed prospective/ retrospective) Methodological quality: 13/19 criteria fulfilled Length of FU: 2 years Losses to FU:	**Dystonic movement disorder (total n=60)** <u>Subtypes</u>: *Inherited dystonia without nervous system pathology*: n=11 (2 male) Age at onset: median 7.7 years (range 0.5–10.4 years) Proportion of life lived with dystonia: median 0.6 (range 0.11–0.97) Age at surgery: median 11.8 years (range 7.3–18.8 years) *Inherited dystonia with nervous system pathology*: n=14 (9 male) Age at onset: median 2.0 years (range 0.5–9.8 years)	Bilateral GPi DBS <u>Pulse generator battery type</u>: Not reported <u>Pulse generator location</u>: Not reported	✓	✓		None to declare

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
1-year: 3/60 (5%) 2-year: 7/48 (15%; only 48 patients had FU ≥2 years)	Proportion of life lived with dystonia: median 0.8 (range 0.07-0.95) Age at surgery: median 11.1 years (range 4.2–17.4 years) *Acquired dystonia*: n=20 (11 male) Age at onset: median 0.2 years (range 0–14.3 years) Proportion of life lived with dystonia: median 0.97 (range 0.14-1.0) Age at surgery: median 10.7 years (range 5.3–17.8 years) *Idiopathic dystonia*: n=15 (10 male) Age at onset: median 2.5 years (range 0.3–13.0 years) Proportion of life lived with dystonia: median 0.8 (range 0.25-0.98) Age at surgery: median 12.2 years (range 6.8–18.6 years)					
Benato et al.[36] Italy Level IV evidence (unclear if prospective or retrospective) Methodological quality: 13/19 criteria fulfilled (2 not applicable) Length of FU: mean 5 years	**Status dystonicus refractory to medication (total n=4)** Age at onset: mean 5.5 years Age at surgery: mean 9 years Duration of status dystonicus: mean 2.3 months Subtypes: *Methylmalonic acidemia*: n=2 (female) *GNAO1* mutation: n=2 (female)	Bilateral GPi DBS (n=3) Bilateral STN DBS (n=1 patient with methylmalonic acidemia) Pulse generator battery type: Not reported Pulse generator location: Not reported	✓	✓		None to declare

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
Losses to FU: 0%						
Koy et al.[40] France and Germany Level IV evidence (prospective) Methodological quality: 9/19 criteria fulfilled (1 not applicable) Longest FU: 10 years Losses to FU: 0%	**Status dystonicus refractory to medication (n=5; 3 male)** Age at onset: mean 4.4 years (range 0-11) Duration of status dystonicus: not stated Age at surgery (n=4): mean 11.5 years (range 6-15) Subtype: *GNA01* mutation	Bilateral GPi DBS Pulse generator battery type: Not reported Pulse generator location: Not reported	✓			None to declare
Lobato-Polo et al.[41] Colombia Level IV evidence (retrospective analysis of prospectively collected data) Methodological quality: 14/19 criteria fulfilled (2 not applicable)	**Status dystonicus refractory to medication (n=2; male)** Age at onset: 0.1 and 1 year Duration of status dystonicus: mean 5.5 days Age at surgery: 8 and 10 years Subtypes: dyskinetic cerebral palsy	Bilateral GPi DBS Pulse generator battery type: Not reported Pulse generator location: nfraclavicular	✓	✓		None to declare

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
Length of FU: 27 months Losses to FU: 0%						
Waak et al[43] Australia and UK Level IV evidence (retrospective) Methodological quality: 9/19 criteria fulfilled (2 not applicable) Length of FU: mean 23.3 months (range 16–28) Losses to FU:0%	**Status dystonicus refractory to medication (n=3; 1 male)** Age at onset: mean 6.3 months (range 3–12) Duration of status dystonicus: Unclear Age at surgery: mean 9.7 years (range 6–13) Subtypes: dyskinetic cerebral palsy and *GNAO1* mutation	Bilateral GPi DBS Pulse generator battery type: Rechargeable (n=2) Pulse generator location: Not stated	✓	✓		None to declare
Case Reports						
Jones et al.[47] Australia Level IV evidence (retrospective)	**Inherited dystonia without nervous system pathology refractory to medication (n=1; female)** Subtype: Myoclonus dystonia Age at onset: 4 years	Bilateral GPi DBS Pulse generator battery type: Not reported	✓		✓	None to declare

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
Methodological quality: Not applicable Length of FU: 12 months Losses to FU: Not applicable	Duration of symptoms: 11 years Age at surgery: 15 years	Pulse generator location: Not reported				
Oterdoom et al.[48] Netherlands Level IV evidence (retrospective) Methodological quality: Not applicable Length of FU: 2.4 years Losses to FU: Not applicable	**Inherited dystonia without nervous system pathology refractory to medication (n=1; male)** Subtype: DYT6 mutation Age at onset: 3.5 years Duration of symptoms: 5.5 years Age at surgery: 9 years	Bilateral GPi DBS Pulse generator battery type: Not reported Pulse generator location: Not reported	✓	✓		None to declare
Skogseid et al.[49] Norway Level IV evidence (retrospective) Methodological quality:	**Inherited dystonia with nervous system pathology refractory to medication (n=1; female)** Subtype: *ACTB* mutation Age at onset: 12 years	Bilateral GPi DBS Pulse generator battery type: Not reported Pulse generator location:	✓			2 of 9 co-authors have received honoraria from Medtronic

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
Not applicable Length of FU: 4 years Losses to FU: Not applicable	 Duration of symptoms: 7 years Age at surgery: 19 years	Not reported				
Brimley and Kershenovich[44] US Level IV evidence (retrospective) Methodological quality: Not applicable Length of FU: 22 months Losses to FU: Not applicable	**Acquired dystonia (n=1; male)** Subtype: cerebral palsy Age at onset: 7 years Duration of symptoms: 2 years Age at surgery: 9 years	Bilateral GPi DBS Pulse generator battery type: Not reported Pulse generator location: Not reported		✓		None to declare
Barbosa et al.[45] Brazil Level IV evidence (retrospective)	**Status dystonicus refractory to medication (n=1; male)** Subtype: DYT1 mutation Age at onset: 13 years	Bilateral STN DBS Pulse generator battery type: Not reported	✓	✓		None to declare

Study Details	Study Population	Intervention	Outcomes Reported[a]			Conflicts of interest
			Efficacy	Safety	Quality of Life	
Methodological quality: Not applicable Length of FU: 10 months Losses to FU: Not applicable	Duration of status dystonicus: 3 months Age at surgery: 15 years	Pulse generator location: Not reported				
Honey et al. [46] Canada Level IV evidence (retrospective) Methodological quality: Not applicable Length of FU: 6 months Losses to FU: Not applicable	**Status dystonicus refractory to medication (n=1; male)** Subtype: *GNAO1* mutation Age at onset: 1.5 years Duration of status dystonicus: 2 months Age at surgery: 10 years	Bilateral GPi DBS Pulse generator battery type: Not reported Pulse generator location: Not reported	✓	✓	✓	None to declare

DBS: deep brain stimulation; FU: follow up; GPi: globus pallidus internus; MPAN: mitochondrial membrane protein-associated; PKAN: pantothenate-kinase-associated neurodegeneration; SD: standard deviation; STN: subthalamic nucleus

[a]Only outcomes measured with an objective rating scale were extracted

[b]Some patients had missing data, but unclear how many

Appendix 3: Quality appraisal results

Table 3.1: Quality appraisal results for the included systematic review using the AMSTAR 2 checklist

Table 3.2: Quality appraisal results for included case series studies using the Institute of Health Economics case series checklist

Table 3.1: Quality appraisal results for the included systematic review using the AMSTAR 2 checklist[32]

Criterion	Elkaim et al.[15]
1. Research questions and inclusion criteria included the PICO[a] components	●
2. Review methods were established a priori	◐
3. Selection of study designs for inclusion clearly explained	●
4. Comprehensive literature search strategy	●
5. Study selection performed in duplicate	●
6. Data extraction performed in duplicate	●
7. List of excluded studies provided with reasons for exclusion	●
8. Included studies adequately described	●
9. Satisfactory technique for assessing risk of bias in included studies	NA
10. Sources of funding reported for included studies	○
11. For meta-analysis, appropriate methods used to combine the results	●
12. For meta-analysis, the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis was assessed	●
13. Risk of bias was accounted for in individual studies when interpreting/discussing the results of the review	●
14. A satisfactory explanation was provided for any heterogeneity observed in the results of the review	●
15. For meta-analysis, an adequate investigation of publication bias was conducted	●
16. Potential sources of conflicts of interest were reported for the review authors	●

[a]PICO = population, intervention, comparator and outcome

Yes: ●; Partial yes: ◐; No: ○; Unclear: ?; Not applicable: NA

Table 3.2: Quality appraisal results for included case series studies using the Institute of Health Economics case series checklist[33]

Criterion		Benato et al.[36]	Canaz et al.[37]	Candela et al.[38]	Koy et al.[40]	Koy et al.[39]	Lobato-Palo et al.[41]	Tustin et al.[42]	Waak et al.[43]
1. Hypothesis/aim/objective clearly stated		●	●	●	●	●	●	●	●
Study design	2. Study conducted prospectively	?	○	●	?	○	◐	◐	○
	3. Multicentre study	○	○	○	●	●	○	○	●
	4. Participants recruited consecutively	?	●	?	?	?	●	●	?
Study population	5. Participant characteristics described	●	●	●	●	●	●	●	●
	6. Participant eligibility clearly stated	●	●	●	●	●	●	●	●
	7. Participants at similar entry point	●	○	○	●	○	●	◐	●
Interventins	8. Intervention(s) clearly described	●	●	●	◐	◐	●	◐	◐
	9. Co-intervention(s) clearly described	●	●	●	○	○	●	○	○
Ou tc c	10. Outcome measures established a priori	●	●	●	○	●	●	●	○

Criterion		Benato et al.[36]	Canaz et al.[37]	Candela et al.[38]	Koy et al.[40]	Koy et al.[39]	Lobato-Palo et al.[41]	Tustin et al.[42]	Waak et al.[43]
	11. Outcomes measured appropriately	●	●	●	◐	●	●	●	○
	12. Outcomes measured before and after the intervention	●	●	●	◐	●	●	●	○
13. Appropriate statistical tests used		NA	NA	NA	NA	●	NA	●	NA
Results/Conclusions	14. Length of follow-up adequate	●	○	○	◐	●	●	●	?
	15. Losses to follow-up reported	●	●	●	●	●	●	●	●
	16. Estimates of random variability provided	NA	●	●	○	●	NA	●	NA
	17. Adverse events reported	●	●	●	●	●	●	○	●
	18. Conclusions supported by results	●	●	●	●	●	●	●	●
19. Competing interests and funding reported		◐	◐	◐	●	●	◐	●	●

Reported: ●; Partially reported: ◐; Not reported: ○; Unclear: ?; Not applicable: N/A

Appendix 4: Efficacy data from primary studies

Study	Diagnosis	Outcome measure	N	Follow up	Preoperative	Postoperative	Absolute or % Change	*p*-value
Inherited dystonia without nervous system pathology								
Canaz et al.[37]	NR	BFMDRS	4	6 months	NR	NR	Median 43% (range 30%–45%)	NR
		SBRS			NA	Mean 1.75 (SD 0.5)	-	
Candela et al.[38]	Primary dystonia	BFMDRS-motor	4	6 months	Mean 42.5 (SD 8.50)	Mean 16.9 (SD 11.14)	Mean 58% (SD 33.4%)	NR
		BFMDRS-function			Mean 12.0 (SD 4.08)	Mean 7.5 (SD 4.65)	Mean 41% (SD 28.9%)	
		Total BFMRDS			**Mean 54.5 (SD 9.60)**	**Mean 24.4 (SD 15.47)**	**Mean 55% (SD 31.3%)**	
	Myoclonus-dystonia	BFMDRS-motor	2	6 months	Range 6–14	Range 1–2	Range 67%–93%	NR
		BFMDRS-function			Range 2–5	Range 0–3	Range 40%–100%	
		Total BFMRDS			**Range 11–16**	**Range 1–5**	**Range 56%–94%**	
		UMRS-action			Range 19–28	Range 0–1	Range 95%–100%	
		UMRS-function			Range 8–10	Range 2–5	Range 50%–75%	
		Total UMRS			**Range 50–72**	**Range 3–18**	**Range 75%–94%**	

Study	Diagnosis	Outcome measure	N	Follow up	Preoperative	Postoperative	Absolute or % Change	*p*-value
Tustin et al.[42]	N=11 *DYT1* (n=5) *GNAO1* (n=1) Myoclonus-dystonia (n=1) Other (n=4)	GMFM-88	11	1 year	Median 78.4 (IQR 31.9–99.3)	Median 94.4 (IQR 81.4–99.4)	Median 6.4 (IQR 0.7–37.7)	0.02
			6	2 years		Median 98.6 (IQR 71.4–99.7)	Median 14.5 (IQR -1.5–31.9)	0.1
Inherited dystonia with nervous system pathology								
Canaz et al.[37]	PKAN	BFMDRS	1	6 months	NR	NR	37.5%	NR
		SBRS			NA	2	-	
	MPAN	BFMDRS	1	6 months	NR	NR	45%	NR
		SBRS			NA	3	-	
	Juvenile parkinsonism	HYS	2	6 months	Mean 2.75	Mean 1	NA	NR
		SBRS			NA	3	-	
Tustin et al.[42]	N=14 PKAN (n=4) GA1 (n=2) Lesch-Nyhan (n=2) Mitochondrial disorder (n=3) Other (n=3)	GMFM-88	13	1 year	Median 29.1 (IQR 15.2–52.7)	Median 38.2 (IQR 26.3–57.7)	Median 0.8 (IQR -2.9–7.8)	0.4
			12	2 years		Median 28.8 (IQR 18.3–54.1)	Median -2.0 (IQR -15.6 to -0.7)	0.06

Study	Diagnosis	Outcome measure	N	Follow up	Preoperative	Postoperative	Absolute or % Change	*p*-value
Acquired dystonia								
Canaz et al.[37]	Cerebral palsy	BFMDRS	1	6 months	NR	NR	41%	NR
		SBRS			NA	1	-	
Tustin et al.[42]	N=20 Cerebral palsy (n=19) Brain injury (n=1)	GMFM-88	19	1 year	Median 31.3 (IQR 15.9–48.9)	Median 34.6 (IQR 18.8–59.1)	Median 0.9 (IQR -2.5–5.6)	0.2
			13	2 years		Median 41.5 (IQR 15.3–50.4)	Median 0.1 (IQR -4.2–3.6)	0.9
Idiopathic dystonia								
Tustin et al.[42]	N=15	GMFM-88	14	1 year	Median 85.8 (IQR 16.8–92.7)	Median 81.3 (IQR 36.1–94.0)	Median 2.2 (IQR -0.9–9.7)	0.06
			10	2 years		Median 71.3 (IQR 39.7–91.0)	Median 5.2 (IQR -3.1–19.2)	0.2

BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; FU: follow up; GA1: Glutaric aciduria type 1; GMFM-88: Gross Motor Function Measure; HYS: Hoehn and Yarh Scale; IQR: interquartile range; MPAN: mitochondrial membrane protein-associated neurodegeneration; N: total number of patients; NA: not applicable; NR: not reported; PKAN: pantothenate kinase-associated neurodegeneration; SBRS: Subjective Benefit Rating Scale; SD: standard deviation; UMRS: Unified Myoclonus Rating Scale

Appendix 5: Safety data from primary studies

Adverse effect	Proportion of patients (n/N)				
Intraoperative outcomes					
No intraoperative complications	1/1[46]				
Postoperative outcomes	**Not stated**	**≤1 month**	**≤3 months**	**≤6 months**	**>6 months**
No postoperative complications	39/39[31, 70-77]				
Surgical site infection	1/3[43]				
Resolved without device removal		1/2[41] 1/5[78]		2/126[79]	
Requiring complete/partial device removal	1/13[80] 3/131[42] 2/12[81]	3/31[82] 1/3[83]	1/1[84]	13/126[79a] 2/5[85] 1/9[37]	1/1[86] 2/31[82b]
	Total 3% (6/156)	Total 12% (4/34)		Total 11% (16/140)	Total 9% (3/32)
Seroma at surgical site resolved without device removal		10/129[79]			
Skin erosion					
Resolved without device removal			1/4[36]		
Requiring complete/partial device removal					3/129[79]
Cerebrospinal fluid collection in pulse generator pocket or scalp burr hole	2/31[82]	1/129[79]			
Asymptomatic intracranial haemorrhage		1/11[87] 1/129[79]			

Adverse effect	Proportion of patients (n/N)				
		Total 1% (2/140)			
Pneumonia		1/5[78]			
Hemiparesis	1/31[82]				
Intolerable stimulation-induced side effects	2/129[79]				
Slurred speech	1/6[88]				2/6[38] 1/1[45]
Mild decline in verbal fluency					1/3[89]
Transient dyskinesia	1/6[88]				
Hardware-related problems					
Technical defect/malfunction (unspecified)	8/131[42] 5/14[80]				
	Total 9% (13/145)				
Inaccurate electrode placement requiring revision	2/31[82]	1/2[90]			1/1[48] 1/1[38]
Lead/electrode migration/ dislodgement requiring complete/partial device removal	1/11[87] 3/129[79] 1/3[43]		1/4[36]		1/1[91] 1/13[80] 1/1[44]
	Total 4% (5/143)				Total 20% (3/15)

Adverse effect	Proportion of patients (n/N)				
Electrode/lead defect/fracture requiring revision	1/11[87] 2/14[80] 16/129[79] 2/31[82] 1/3[83]				1/2[90] 1/5[78] 1/1[48]
	Total 12% (22/188)				Total 38% (3/8)
Loss of effect requiring revision/removal					2/2[90]
Impulse generator migration					
Short/tight extension lead due to growth	5/129[79]				
Pain associated with lead/impulse generator location					1/1[92]
Recharger malfunction requiring replacement	49/129[79]				
Impulse generator switched off unexpectedly	9/129[79]				1/6[38]

[a]8% for children younger than 7 years (2/26)

[b]Hardware infection occurred in 57% (4/7) of children younger than 10 years, whereas the infection rate for children older than 10 years was 0% (p=0.001), regardless of diagnosis.

Note: Nearly all of the surgeries were first-time DBS operations

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