Check for updates

REVIEW

CME

# Current Therapies and Therapeutic Decision Making for Childhood-Onset Movement Disorders

Shekeeb S. Mohammad, PhD,[1,2] Simon P. Paget, FRACP,[3] and Russell C. Dale, PhD[1,2*]

[1]*Kids Neuroscience Centre, The Kids Research Institute at the Children's Hospital at Westmead, Brain and Mind Centre, Faculty of Medicine and Health, University of Sydney, Westmead, NSW, Australia*
[2]*Movement Disorders Unit, T.Y. Nelson Department of Neurology, the Children's Hospital at Westmead and Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[3]*Kids Rehab, the Children's Hospital at Westmead and Sydney Medical School, University of Sydney, Sydney, NSW, Australia*

**ABSTRACT:** Movement disorders differ in children to adults. First, neurodevelopmental movement disorders such as tics and stereotypies are more prevalent than parkinsonism, and second, there is a genomic revolution which is now explaining many early-onset dystonic syndromes. We outline an approach to children with movement disorders starting with defining the movement phenomenology, determining the level of functional impairment due to abnormal movements, and screening for comorbid psychiatric conditions and cognitive impairments which often contribute more to disability than the movements themselves. The rapid improvement in our understanding of the etiology of movement disorders has resulted in an increasing focus on precision medicine, targeting treatable conditions and defining modifiable disease processes. We profile some of the key disease-modifying therapies in metabolic, neurotransmitter, inflammatory, and autoimmune conditions and the increasing focus on gene or cellular therapies. When no disease-modifying therapies are possible, symptomatic therapies are often all that is available. These classically target dopaminergic, cholinergic, alpha-adrenergic, or GABAergic neurochemistry. Increasing interest in neuromodulation has highlighted that some clinical syndromes respond better to DBS, and further highlights the importance of "disease-specific" therapies with a future focus on individualized therapies according to the genomic findings or disease pathways that are disrupted. We summarize some pragmatic applications of symptomatic therapies, neuromodulation techniques, and some rehabilitative interventions and provide a contemporary overview of treatment in childhood-onset movement disorders. © 2019 International Parkinson and Movement Disorder Society

**Key Words:** dystonia; DBS; levodopa; movement; therapy; treatment

Movement disorders of childhood follow similar classification systems to adults. However, neurodevelopmental movement disorders such as tics and stereotypies are most prevalent, unlike parkinsonism, which is rare in children. This review starts with a clinical approach to the child with abnormal movements and then discusses the therapeutic principles.

## Guiding Principles

The approach to the child with a movement disorder should include the following considerations (summarized in Fig. 1):

1. **What is the movement disorder phenomenology and what process does this represent?** This is an essential starting point for the clinician, and diagnostic and therapeutic pathways will differ according the movement phenotype. For example, the child with stereotypies or tics will have a different therapeutic pathway to the child with dystonia.

***Correspondence to**: Prof. Russell C. Dale, Clinical School, the Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia; E-mail: russell.dale@health.nsw.gov.au

Full financial disclosures and author roles may be found in the online version of this article.

**Relevant conflicts of interest/financial disclosures:** Nothing to report.

**Received:** 5 February 2019; **Accepted:** 12 February 2019

**Published online 28 March 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27661**

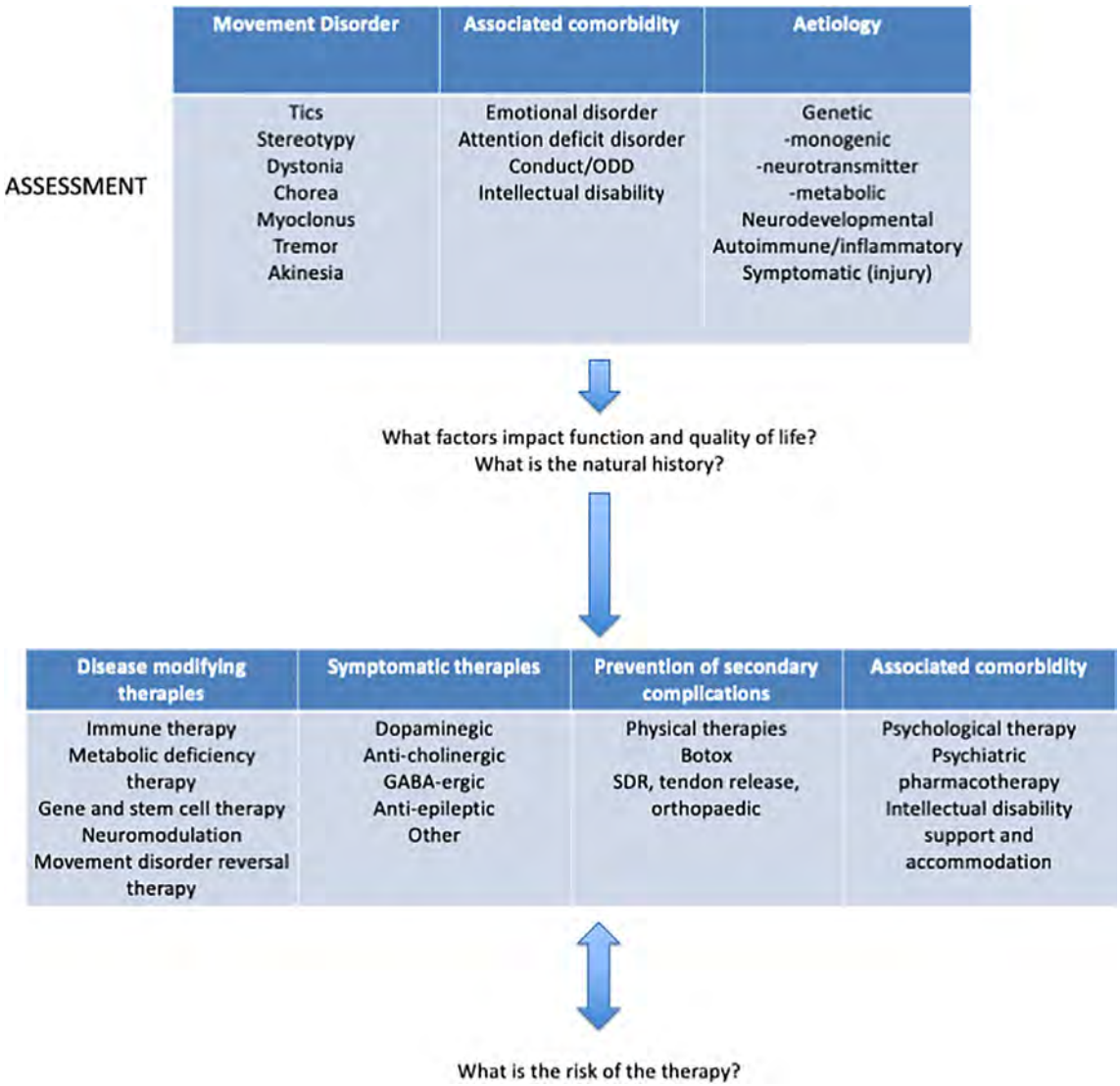


**FIG. 1.** Approach to therapeutic decision making in children with movement disorders. ODD = Oppositional defiant disorder, GABA = Gamma amino butyric acid, SDR = Selective dorsal rhizotomy. [Color figure can be viewed at wileyonlinelibrary.com]

2. **Can we treat the underlying process, or is symptomatic treatment the only option?** This is arguably one of the most important issues in movement disorder treatment. The clinician should always ask the question, "Is there a modifiable disease process that can be treated in this individual?" This is particularly true for neurotransmitter disorders, which can be treated with levodopa or other biochemical replacement. Defining treatable metabolic or vitamin deficiency is likewise a priority. Furthermore, defining reversible autoimmune or immunological processes is important, because the priority should be treating the underlying disease process (immune therapy), rather than the symptoms (movement disorder medications). Understanding the disease process is also essential with the emergence of gene therapies and neuromodulation techniques, including deep brain stimulation (DBS). For the latter, it is increasingly evident that certain genetic dystonias are more likely to respond to DBS than symptomatic dystonias.
3. **What is the functional impact of the movement disorder?** Understanding the functional impact of the movement disorder is essential. The young child with tics is often not impaired or troubled by their excessive movements, whereas the parent may be more concerned about developmental and social consequences. Therefore, education and understanding may be all that is required in some children with movement disorders. By contrast, in some children with severe Tourette's disorder, which impacts quality of life, or dystonia, which is functionally impairing, the family and clinician may be more motivated to treat. When a commitment is made to trial a pharmacological or nonpharmacological treatment, goal-orientated individualized outcome measures (e.g., Canadian Occupational Performance Measure,

Goal Attainment Scaling)[1] can provide a useful measure of treatment effect or failure. The model of functioning and disability proposed in the World Health Organization's International Classification of Functioning, Disability and Health (ICF)[2] can be useful by promoting goals of intervention that improve function ("activity") and social inclusion ("participation").

4. **How effective is the treatment in this disease, and what is the "risk versus benefit" of the therapy?** This is an essential consideration given that the adverse effects of treatment can be worse than the movement disorder itself. The clinician needs to weigh up the functional impact of the movement disorder with the risk of the therapy. For most therapies, side effects are transient and reversible (e.g., sedation with clonidine or guanfacine). However, there are potential risks of permanent adverse effects from some interventions, such as the risk of tardive dyskinesia with neuroleptics, risk of brain injury with DBS, or the risk of infectious side effects of immunosuppressive therapy.
5. **Is the movement disorder the primary impairing problem, or are other associated problems of more concern?** The clinician needs to be aware of potential comorbidities (e.g., intellectual or psychiatric manifestations), which are prevalent in pediatric movement disorders. This is discussed in more detail below.
6. **What is the risk of doing nothing?** Understanding the natural history of disease is central to therapeutic decision making. For example, in autoimmune conditions, such as opsoclonus myoclonus ataxia syndrome, untreated and in the relapsing form, there is a 70% risk of permanent motor or cognitive disability,[3-5] whereas intensive immune therapy has significantly reduced this risk.[4] Furthermore, status dystonicus is a recognized life-threatening emergency often requiring intensive care management. Although the evidence is less definitive, there is also evidence that early dopaminergic treatment of neurotransmitter conditions, such as tyrosine hydroxylase deficiency, can improve long-term outcomes,[6] and there is general agreement that early treatment of dystonia can reduce orthopedic complications as well as pain, and improve function.

## Disease-Modifying and Disease-Specific Therapies

We begin with consideration of conditions that, although rare, have highly specific, potentially curative therapies.

### Movement Disorders in Inborn Errors of Metabolism

There are a number of movement disorders that are attributed to specific, identified metabolic defects.[7] A prime example are monogenic, dopamine deficiency syndromes such as Segawa disease (GTP cyclohydrolase deficiency). These are reviewed in detail elsewhere with more detailed dosing guides for L-dopa and other medications in these syndromes.[8-10] Neurotransmitter diseases should be suspected when there is unexplained dystonia-akinesia along with other symptoms, such as dysautonomia or diurnal fluctuation, and can be diagnosed on neurotransmitter analysis, genomic investigations, or suspected with an appropriate trial of dopamine replacement therapy. Recent reviews[7,11] provide a good overview of other metabolic syndromes that can manifest with movement disorders. In addition, the web-based resource, www.treatable-id.org,[12] outlines several treatable causes of dystonia and other neurological presentations. While several disorders mentioned in the above resources are modifiable with specific interventions, we highlight those disorders in Table 1 where a disease-modifying intervention can cause significant improvement of movement disorders, plateauing of disease course, or complete remission. There are other treatable inborn errors of metabolism that may manifest with movement disorders in adulthood or may present with spastic diplegia or ataxia, which are discussed in comprehensive reviews.[11,13]

### Immune-Mediated Disorders

It is important to recognize immune-mediated conditions that present with movement disorders in children, given that they are amenable to immune-modulatory therapies. Opsoclonus myoclonus ataxia syndrome is a recognizable condition which is associated with neural crest tumors in 50% of cases,[39] and the use of corticosteroids, intravenous immunoglobulin, rituximab, and cyclophosphamide has changed the natural history of this disease.[4] As is true for many conditions, early recognition and treatment and inducing a complete clinical remission and minimizing relapse is the therapeutic aim.[5] Movement disorders are a cardinal feature of anti–N-methyl D-aspartate receptor (NMDAR) encephalitis, the most common autoimmune encephalitis in children, and the use of immune-modulatory therapies is improving the mortality of this disease, with early therapy leading to better outcomes.[40,41] Basal ganglia encephalitis is a rare inflammatory encephalitis presenting with dystonia-akinesia and inflammatory lesions of the basal ganglia.[42] Early corticosteroids and intravenous immunoglobulin can improve outcomes by preventing irreversible basal ganglia atrophy or sclerosis with associated motor and psychiatric sequelae.[43] Sydenham chorea (SC) is a poststreptococcal autoimmune neuropsychiatric syndrome, and although most patients improve, many can be left with some residual chorea or psychiatric predisposition.[44,45] Although not

**TABLE 1.** Clinical phenotype and disease-specific treatment of selected metabolic disorders

| Disease Category (as per Vademicum Metabolicum)[13] | Metabolic Disorder (Gene) | Movement Disorder Phenotype in Childhood | Other Clinical Features | Disease-Specific Treatment |
|---|---|---|---|---|
| Amino acid and peptide metabolism | Glutaric aciduria type 1 (GCDH) | Dystonia | Episodic encephalopathy<br>Macrocephaly<br>Spasticity | Lysine restricted diet<br>Carnitine supplements[14] |
| | Hartnup disease (SLC6A19) | Dystonia | Ataxia<br>Photodermatitis | High-protein diet |
| | Homocytinuria (CBS) | Dystonia | Marfan-like appearance<br>Seizures<br>Myopia<br>Lens dislocation<br>Hypercoagulable state | Methionine restriction<br>Pyridoxine, folic acid, hydroxycobalamin, vitamin C, and betaine supplementation[15] |
| | Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (SLC25A15) | Dystonia | Episodic encephalopathy<br>Spasticity<br>Coagulopathy | Ornithine supplementation<br>Protein-restricted diet Sodium benzoate[16] |
| | Maple syrup urine disease (DBT, BCKDHB, BCKDHA) | Dystonia | Ataxia<br>Intellectual disability<br>Encephalopathic crises<br>Maple syrup smell from urine (untreated) | Leucine-restricted diet[17] |
| | Methylmalonic aciduria (MMAA, MMAB, MMACHC, MMADHC, LMBRD1, MUT) | Dystonia | Developmental delay<br>Intellectual disability<br>Encephalopathic crises | Protein-restricted diet<br>Carnitine supplementation[18] |
| | Phenylketonuria (PAH) | Dystonia<br>Parkinsonism (untreated) | Intellectual disability<br>Seizures<br>Spasticity (untreated) | Phenylalanin-restricted diet<br>BH4 and amino acid supplementation[19] |
| | Propionic acidemia (PCCA, PCCB) | Dystonia | Developmental delay<br>Intellectual disability<br>Encephalopathic crises<br>Seizures<br>Optic atrophy | Protein-restricted diet<br>Carnitine supplementation[20] |
| | Molybdenum cofactor deficiency (MOCS1, MOCS2) | Dystonia, parkinsonism | Infantile epileptic encephalopathy<br>Psychomotor retardation<br>Microcephaly<br>Lens dislocation | Cyclic pyranopterin monophosphate[21] |
| Bile acid synthesis | Cerebrotendinous xanthomatosis (CYP27A1) | Dystonia, parkinsonism | Ataxia<br>Hepatitis<br>Psychomotor retardation<br>Diarrhea<br>Cataract<br>Tendon xanthoma, atherosclerosis<br>Dementia | Chenodeoxycholic acid[22] |
| Energy metabolism | Creatine deficiency (GAMT) | Dystonia | Intellectual disability<br>Seizures | Creatine supplementation[23] |
| | Pyruvate dehydrogenase deficiency (PDHA1, PDHX, DLAT, ECHS1) | Dystonia, episodic dystonia/dyskinesia | Spasticity<br>Intellectual disability<br>Seizures<br>Autistic behavior<br>Self-mutilation | Ketogenic diet[24] |
| Lipid storage | Neuronal ceroid lipofuscinosis (CLN2) | Progressive dystonia, myoclonus | Spasticity<br>Epilepsy<br>Visual impairment | Intraventricular infusion of cerliponase alfa-recombinant human tripeptidyl peptidase-1 every 2 weeks lifelong[8] |
| Lysosomal metabolism | Gaucher disease type 3 (GBA) | Parkinsonism, chorea, epileptic and nonepileptic myoclonus | Psychomotor retardation<br>Horizontal supranuclear gaze palsy<br>Seizures<br>Spasticity | Enzyme replacement therapy with glucocerebrosidase[25] |

*(Continues)*

**TABLE 1.** Continued

| Disease Category (as per Vademicum Metabolicum)[13] | Metabolic Disorder (Gene) | Movement Disorder Phenotype in Childhood | Other Clinical Features | Disease-Specific Treatment |
|---|---|---|---|---|
| | | | Dementia<br>Pancytopenia | |
| | Niemann-Pick C (NPC1, NPC2) | Dystonia<br>Chorea<br>Parkinsonism | Dementia<br>Psychosis<br>Supranuclear gaze palsy | Miglustat[26] |
| Metabolism of trace elements and metals | Manganese transport disorders (SLC30A10 and SLC39A14) | Dystonia | Spasticity<br>Psychomotor retardation<br>Polycythemia and hepatic dysfunction in SLC30A10 | Chelation with $CaNa_2EDTA$[6,7] |
| | Wilson's disease (ATP7B) | Dystonia, parkinsonism, chorea | Dysarthria<br>Hepatic dysfunction, psychiatric features | Chelation with D-penicillamine, trientine, or tetrathiomolybdate[27,28]<br>Zinc acetate/sulphate |
| Neurotransmitters | 6-Pyruvoyl tetrahydropterin synthase deficiency (PTS) | Dystonia, parkinsonism, chorea | Intellectual disability<br>Psychiatric features (OCD, depression, panic attacks)<br>Hypersomnolence<br>Dysautonomia<br>Seizures can occur | BH4<br>L-dopa[4] |
| | Aromatic L-amino acid decarboxylase deficiency (DDC) | Dystonia, prominent oculogyric crises, choreoathetosis | Intellectual disability<br>Seizures<br>Insomnia | Dopamine agonists<br>MAO inhibitors<br>Pyridoxine[29] |
| | Dihydropteridine reductase deficiency (QDPR) | Dystonia, chorea, tremor, parkinsonism | Bulbar dysfunction<br>Hypersomnolence<br>Dysautonomia | L-dopa<br>5-HTP<br>Calcium folinate (folinic acid)[7] |
| | Dopamine transporter deficiency syndrome (SLC6A3) | Progressive dystonia parkinsonism, dyskinesia | Global developmental delay<br>Feeding difficulty<br>Irritability | Dopamine agonists[7,30] |
| | GABA transaminase deficiency (ABAT) | Chorea | Hypersomnolence<br>Seizures<br>Global developmental delay Encephalopathy<br>Macrosomia | Flumazenil[5] |
| | Glucose transporter deficiency (SLC2A1) | Episodic/exercise-induced dystonia/dyskinesia, ataxia, spasticity, dystonia | Intellectual disability<br>Seizures | Ketogenic diet[31]<br>Triheptanoin[32] |
| | GTP cyclohydrolase deficiency–autosomal dominant (GCH) | Exercise or movement induced dystonia, parkinsonism | — | L-dopa[7,9] |
| | GTP cyclohydrolase deficiency–autosomal recessive (GCH) | Hypotonia<br>Dystonia | — | L-dopa[7,9] |
| | Sepiapterin reductase deficiency (SPR) | Dystonia | Hypersomnia | L-dopa<br>5-HTP[9,10] |
| | Succinic semialdehyde dehydrogenase deficiency (ALDH5A1) | Dystonia | Hypotonia<br>Ataxia<br>Intellectual disability | Vigabatrin[33] |
| | Tyrosine hydroxylase deficiency (TH) | Dystonia | Spastic diparesis/quadriparesis | L-dopa[34] |
| | Vesicular monoamine transporter 2 deficiency (SLC18A2) | Dystonia<br>Oculogyric crises | Hypotonia<br>Psychomotor retardation<br>Dysautonomia | Dopamine agonists[35] |
| Vitamins/cofactors metabolism | Biotinidase deficiency (BTD) | Dystonia | Spasticity<br>Ataxia<br>Seizures<br>Skin rashes<br>Hair loss | Biotin supplementation[36] |

*(Continues)*

**TABLE 1.** Continued

| Disease Category (as per Vademicum Metabolicum)[13] | Metabolic Disorder (Gene) | Movement Disorder Phenotype in Childhood | Other Clinical Features | Disease-Specific Treatment |
|---|---|---|---|---|
| | Biotin-thiamine–responsive basal ganglia disorder (SLC19A3) | Dystonia | Immune deficiency<br>Episodic encephalopathy<br>Spasticity<br>Seizures can occur | Thiamine<br>Biotin[37] |

5-HTP, 5 hydroxy tryptophan; BH4, tetrahydrobiopterin; EDTA, ethylene diamine tetra acetic acid; MAO, monoamine oxidase.

a standard of care, it is our practice to use one course of intravenous corticosteroid and immunoglobulin in SC, and there is some support for this in the literature.[46,47] Although symptomatic medications can reduce the symptoms of immune-mediated movement disorders, we believe disease-modifying immunotherapy should be the mainstay of treatment (Table 2).

## Gene Therapy and Other Disease-Modifying Therapies

The treatment approach to monogenic neurological disorders has seen significant advances with therapies that can modify the underlying disease process genetically or by modifying intracellular signaling. Although the term gene therapy was conventionally used for the process of transferring DNA into a cell using a vector to edit cellular DNA, gene therapies or gene replacement strategies are now broadly classified with other interventions such as cell-based therapies and tissue engineered products as "advanced therapy medicinal products."[53] Recently, remarkable advances are exemplified by the use of oligonucleotides to alter protein expression using nusinersen in spinal muscular atrophy, summarized along with other RNA-based approaches in a recent review.[54] This shows what may be possible in other monogenic neurological conditions, including movement disorders.

Gene therapy trials using viral vectors are now in extension phases with promising results in improvement of movement disorder and motor function in early clinical studies of *AADC* deficiency.[55] In some other monogenic disorders, better understanding of disease mechanisms has led to trials of interventions that target disease mechanisms. An example is the use of JAK inhibitors or reverse-transcriptase inhibitors trialled in Aicardi-Goutieres syndrome presenting with progressive dystonia and progressive spinal paraplegia, which

**TABLE 2.** Clinical phenotype, disease-specific and symptomatic treatment of major immune-mediated movement disorders in children

| Immune-Mediated Disorder | Movement Disorder Phenotype | Other Clinical Features | Disease-Specific Treatment | Symptomatic Treatment of Movement Disorder |
|---|---|---|---|---|
| Opsoclonus myoclonus ataxia syndrome | Myoclonus, opsoclonus | Ataxia<br>Irritability | Corticosteroids/ACTH<br>Rituximab, IVIg, cyclophosphamide | Piracetam has modest effect.[47]<br>Sedative medications in irritable phase |
| Anti-NMDAR encephalitis | Mixed movement disorder phenotype with prominent stereotypical movements and orofacial dyskinesia[48,49] | Encephalopathy<br>Seizures<br>Psychiatric symptoms<br>Sleep disturbance | Corticosteroids, IVIg, plasma exchange, rituximab<br>Tumor removal where present | Sedative medications to modify sleep cycle<br>Anticonvulsants<br>Antipsychotics for agitation but risk of neuroleptic malignant syndrome[50] |
| Autoimmune basal ganglia encephalitis | Dystonia, parkinsonism, chorea | Encephalopathy<br>Hypersomnolence | Corticosteroids, IVIg | Anticholinergics, clonidine, or L-dopa may partially benefit some patients. |
| Sydenham's chorea | Chorea | Emotional lability<br>Psychiatric symptoms<br>Other features of rheumatic fever may be present. | Corticosteroids, IVIg[46] | Carbamazepine<br>Sodium valproate[46]<br>Antipsychotics like haloperidol are effective (few reports note extrapyramidal adverse effects and later risk of parkinsonism).[51] |
| Stiff person spectrum disorders | Rigidity, stimulus responsive myoclonus | Encephalopathy | Corticosteroids, IVIg, rituximab | Benzodiazepines<br>Oral or intrathecal baclofen |

ACTH, adrenocorticotrophic hormone; IVIg, intravenous immunoglobulin.

target cellular processes, and preliminary data suggest reduced disease activity.[56] Ongoing clinical trials of disease-modifying or gene therapies in conditions associated with movement disorders in children are summarized below in Table 3, and a complete list of current, approved gene therapy trials is listed by Ginn and colleagues[57] and updated by the World Health Organization[58] and the NIH.[59]

### Movement Disorder Reversal Therapies

The Comprehensive Behavioral intervention for Tics (CBIT) is a behavioral intervention that requires the child to identify the premonitory urge and create competing responses (habit reversal training) and over time increase the tolerance to the urge (exposure with response prevention). This therapy was shown to be effective in a randomized controlled trial, and CBIT is being recommended as first-line therapy[69-71] for children with tic disorders. Online delivery of the therapy is being tested, which may increase the availability of CBIT, given that this is currently limited to locations with a trained psychologist. Although CBIT is, in theory, a disease-modifying therapy, this is yet to be proven at a pathophysiological level. Also, uptake of the therapy is limited by cognitive ability and motivation, precluding its use in young children and those with intellectual disability or severe autistic features.

## Symptomatic Therapies

For many conditions where there is no definable pathogenic variant, or the disease process is unidentified or unmodifiable, symptomatic therapies are the only option, which may result in clinical improvement. These symptomatic therapies are described according to their neurochemical target. Specific tiered evidence and detailed dose guides for various medications can be found in a recent review by Koy and colleagues.[72]

### Dopaminergic Therapies

Dopamine is a central neurotransmitter in the therapeutics of movement disorders, given its central role in the regulation of movement and behavior. The clinician should be always vigilant to the rare possibility of a neurotransmitter disorder in which dopamine replacement can result in full resolution of dystonic or akinetic phenomena. Dopa-responsive dystonia (DRD) has typical clinical features of emergent limb dystonia, exacerbated by exercise and with diurnal variation. Dopamine replacement at doses around 5 mg/kg/day is typically curative. Tyrosine hydroxylase deficiency can present with akinesia, hypotonia, and oculogyric crises in infancy, and patients can become dyskinetic at low doses, but, on slow increasing regimens, may respond impressively, typically requiring higher doses than

**TABLE 3.** Disease-specific gene or cellular therapies for monogenic conditions that can present with childhood-onset movement disorders*

| Genetic Disorder | Movement Disorder | Intervention | Status of Intervention |
|---|---|---|---|
| AADC deficiency | Dystonia, prominent oculogyric crises, choreoathetosis | AAV-delivered gene therapy targeted to the SN | Motor function improvement in phase 1 and 2 clinical trials and some phase 1 and 2 extension trials are presently recruiting patients.[58] |
| Aicardi-Goutieres syndrome | Dystonia (in various subtypes, particularly ADAR mutations—AGS6)[60]<br>Spastic paraparesis (in various subtypes)[60,61] | Reverse-transcriptase inhibitors<br>Janus kinase 1/2 block | Reduced interferon signaling and improved cerebral blood flow (open label study of 8 patients)[56]<br>Single case showing clinical improvement[62] |
| Ataxia telangiectasia | Dystonia, choreoathetosis, ataxia, oculomotor apraxia[63] | Intraerythrocyte dexamethasone | Clinical improvement in phase 1/2 trials. Currently ongoing multicenter extension phase[58,64] |
| Criggler-Najjar syndrome | Dystonia, choreoathetosis (dyskinetic CP) | Intravenous injection of AAV-delivered gene therapy | Phase 1 and 2 clinical trial recruiting based on results of normalization of bilirubin levels in animal studies[65] |
| Neuronal ceroid lipofuscinosis | | | |
| CLN2 | Ataxia, epileptic and nonepileptic myoclonus, chorea[44,66] | AAV-delivered gene therapy | Ongoing phase 1/2 trial NCT01414985[59] |
| CLN6 | Ataxia, myoclonus, parkinsonism[67] | AAV-delivered gene therapy | Ongoing phase 1/2 trials NCT02725580[59]<br>Other past trials summarised by Mole et al.[68] |

*We have not outlined similar gene therapy or cellular therapy trials that have already been completed with negative results or may be in a preliminary stage, for example with other subtypes of ceroid lipofuscinosis.[68]
AADC, aromatic acid decarboxylase; AAV, adeno-associated virus; AGS, Aicardi-Goutieres syndrome.

DRD, with doses up to 10 mg/kg/day or more. Other neurotransmitter disorders require dopamine replacement plus other neurotransmitters or pterin replacement and are reviewed in detail elsewhere.[8,10] These neurotransmitter conditions are the reason all children with unexplained dystonia or akinesia should have a L-dopa trial, particularly in the context of a normal MRI and suggestive clinical features, as above. Complete dopa responsiveness is suggestive of a primary neurotransmitter condition and sometimes other monogenic disorders such as PARKIN deletions[73]; however, varying dopamine responsiveness can be observed in some other genetic nonprogressive disorders (DNAJC12,[74,75] DYT11, paroxyxmal kinesigenic and nonkinesigenic dyskinesia, and pyruvate dehydrogenase complex deficiency),[76,77] genetic-progressive disorders (ataxia telangiectasia,[78] chorea acanthocytosis, DJ-1,[79] FBX07,[80] Kufor-Rakeb disease,[80] nuclear inclusion body disease,[81] PINK1,[82] pantothenate kinase associated neurodegeneration, PLA2G6 associated neurodegeneration,[80] pontocerebellar hypoplasia type 2,[76] SCA2, SCA3, SOX6,[83] SPG11,[84-86] and xeroderma pigmentosum[76]), and, to a lesser extent, in acquired disorders such as movement disorders with lupus, organophosphate poisoning, subacute sclerosing panencephalitis, postencephalitic dystonia,[76] or extrapontine myelinolysis. The role of L-dopa in management of dystonic cerebral palsy (CP) is questionable and results from previous studies are contradictory.[87]

Given the chance of variable benefits in some cases with different underlying disorders, an L-dopa trial is still commonly practised. Though relatively safe, families need to be counseled about commonly reported adverse events with dopamine (nausea, vomiting, and sometimes headache, constipation, somnolence, or insomnia).[88] Troublesome dopa-induced dyskinesia can occur in GTP cyclohydrolase deficiency, tyrosine hydroxylase deficiency, PARKIN deletions, and FBX07, and clinical worsening of dystonia can occur in some conditions such as reported in Lesch-Nyhan syndrome.[89] L-dopa needs to be stopped at least 48 hours before a lumbar puncture to avoid falsely high/normal homovanillic acid levels. It is also important to objectively define baseline movement disorder and motor dysfunction and set a target duration such as 1 to 3 months for an L-dopa trial (by when most monoamine disorders would respond)[90,91] aiming to reach 4 to 5 mg/kg/day dosing.

Dopamine agonists such as pramipexole or ropinirole are not commonly used in the paediatric age group. They are suggested as an option for treatment of monoamine disorders, particularly in cases of PTPS or AADC deficiency, where L-dopa may lead to on-off phenomena or other adverse effects.[8,92] They have been reported to show benefit in some disorders, such as brain dopamine-serotonin vesicular transport disease[36] or dopamine transporter deficiency syndrome,[93] where L-dopa was noted to be ineffective.

Dopamine depletion using tetrabenazine, which blocks vesicular monoamine transporter, is typically used when there is a theoretical dopamine excess, typically in patients with chorea or dyskinetic movements. There is some emerging evidence for use in severe dyskinetic movement exacerbations observed in patients with GNAO1-related movement disorders,[94] in tardive dyskinesia[95] and in status dystonicus in general.[96,97] Tetrabenazine or deutetrabenazine are also used in Tourette's syndrome,[98,99] particularly in adults, although in our experience these are less well tolerated compared to the neuroleptics.

Dopamine blockade with neuroleptics is used in patients with tics and other hyperkinetic movement disorders such as chorea. Risperidone is the neuroleptic with most evidence in tic disorders and has high affinity for dopamine receptors.[100] Aripiprazole also has good evidence of effect in tic and Tourette's syndrome and is a partial dopamine agonist.[101] Other neuroleptics, such as sulpiride, arisulpiride, and pimozide,[102] are used to treat tic disorder in parts of the world, although the best evidence of effect exists for risperidone and aripiprazole in Tourette's syndrome. All neuroleptics, including aripiprazole, can cause extrapyramidal adverse effects.[103] Dopamine blocking agents are often held responsible for tardive dystonia. However, neuroleptics are still used in the treatment of status dystonicus[96,97] and have been paradoxically noted to relieve dystonia in anecdotal reports. Underlying disease processes, such as anti-NMDAR encephalitis[51] or Sydenham chorea[47] or genetic makeup,[104,105] may confer vulnerability to extrapyramidal adverse effects from neuroleptics. Our practice is to avoid their use in children with dystonia and use them cautiously in children with other movement disorders and psychiatric comorbidity.

## Anticholinergics

Anticholinergics are trialed in patients with dystonia, including monogenic disorders and dystonic CP. They are the only symptomatic movement disorder medications that have been examined in randomized trials in children with noted benefit in some patients,[106] while other trials[107,108] have been unable to document a clear benefit. The summary of evidence from literature, particularly from the dystonic CP population,[87] suggests a dose- and duration-dependent benefit in functional abilities, particularly upper limb function.[109] Benztropine and benzhexol (trihexiphenidyl) are centrally acting anticholinergics that are commonly used to treat movement disorders. The rationale for these agents is based on the hypotheses of relative hyperactivity of cholinergic interneurons in dystonia[110] and the role of these interneurons in abnormal synaptic plasticity.[111] In the authors' experience, trihexiphenidyl can be highly effective in some patients, but intolerable in others.

Trihexiphenidyl is typically started at a low dose (0.25 mg once per day) and increased every 3 to 7 days to 2 mg twice per day and can be increased further in older children. Some reports suggest that children may benefit from, and tolerate as much as, 50 to 100 mg/day,[112] but this is rarely the case in our experience, mainly attributed to dose-limiting adverse effects. In some genetic dystonias, such as DYT1[112] (and personal experience) or DYT11,[113] trihexiphenidyl can be highly effective. Adverse events are common and include anticholinergic side effects such as constipation, ileus, dry mouth, blurred vision, urinary retention, and cardiovascular alterations.[87,108] In addition, anticholinergics can cause confusion, depression, personality change, and cognitive issues.[106,114]

Benztropine seems to find more favor in psychiatric settings compared to trihexiphenidyl for treatment of drug-related dystonia. Generally, anticholinergics are not recommended for treatment of tardive dyskinesia[115] except in the setting of tardive dystonia.[116] They can also worsen movement disorders in some children with choreoathetosis.[117]

## GABAergic Agents

Gamma amino butyric acid (GABA) is one of the primary inhibitory neurotransmitters and has been an attractive therapeutic target in movement disorders. Baclofen is a GABA agonist and is often used in children with spasticity and some dystonic syndromes. Oral baclofen is commonly used in children with CP with a mixed dystonic/spastic picture, helping manage high tone and associated pain; however, its efficacy is not well supported by the literature.[118,119] Starting doses are 5 or 10 mg once per day increasing to 30 to 40 mg three times per day, with sedation being the main limiting factor. Benzodiazepines, such as clobazam, clonazepam, diazepam, and midazolam, are GABA agonists and are often needed in emergent settings such as status dystonicus,[97] useful to sedate, reduce anxiety, induce sleep, and reduce tone. They are occasionally useful in other children with severe dystonia, in children with severe exacerbations of tics or self-injurious behavior; however, they have the limitation of habituation and are best used for short duration. Benzodiazepines are also useful in catatonia.[120]

## Alpha Agonists

Clonidine is an alpha agonist and commonly used for the treatment of tic disorders with attention deficit hyperactivity disorder (ADHD). Clonidine can also help with sleep induction, calming, and reducing anxiety. Other than tic disorders, and treating psychiatric comorbidity, clonidine can be useful in status dystonicus, such as patients with GNAO1 dyskinetic exacerbations.[121-123] In patients with tic disorders, clonidine may be used only at night (50–100 μg), or in a twice-daily regimen. In emergency settings, such as status dystonicus, clonidine can be used more regularly, such as 50 μg every 2 hours (dose equivalents up to 2.5 μg/kg/hr[121]) with increased doses at night, to induce sedation. Oral clonidine can be effective and reduce the need for intravenous sedation in status dystonicus. Other alpha agonists that are used for movement disorder treatment are guanfacine and dexmedetomidine. Guanfacine has less sedative effects compared to clonidine and can be trialed for outpatient indications such as comorbid tics and ADHD.[124-126] The effects of oral alpha agonists on both tics and ADHD are modest. Dexmedetomidine is usually restricted to intensive care or perioperative settings such as in management of status dystonicus[127] or the florid stage of anti-NMDAR encephalitis.[51,128] It offers the benefit of sedation without respiratory depression and less hemodynamic adverse effects.

## Antiepileptics

Antiepileptics such as carbamazepine are used in specific movement disorders such as paroxysmal kinesigenic dyskinesia (Table 4), but are also sometimes used in patients with chorea or myoclonus. Sodium valproate and carbamazepine may have some effect on the chorea of Sydenham's chorea in observational studies.[129-131] Zonisamide has been shown to be effective in a randomized controlled trial in myoclonus dystonia,[132] and topiramate has been proposed to be useful in cases of GNAO1 dyskinetic syndromes[133] and in reduction of tics in Tourette's disorder.[134] Primidone has been effective for the treatment of familial (essential) tremor.[135-137]

Agents such as gabapentin and pregabalin are related medications, which act on the alpha2-delta protein, an auxiliary subunit of voltage-gated calcium channels. They were initially designed as antiepileptics, but have found a potential use in psychiatry as antianxiety agents[138] for treatment of self-harm behavior[139] and neuropathic pain and have been used off label in dystonia[140] and dyskinetic movement disorders.[141] Gabapentin has been noted to be beneficial in children with severely disabling dystonia,[142] particularly if manifesting with pain or dystonic spasms.

## Cannabinoids

The role of cannabinoids is commonly discussed, but there has only been formal introduction of these products for epilepsy and pain management. Recently, a systematic review[143] examined the evidence for use of cannabinoids in movement disorders, including 21 publications ranging from case series to trials. The movement disorders treated included Tourette's disorder,[144-146] parkinsonism,[147,148] dystonia,[149-152] tremor,[153] and Huntington's disease.[154,155] Although some studies have

**TABLE 4.** Treatment of episodic or paroxysmal movement disorders along with reported monogenic associations

| Episodic Movement Disorder Syndrome | Genetic Associations | Phenotypic Overlap | Treatment |
|---|---|---|---|
| Paroxysmal kinesigenic dyskinesia | PRRT2 (>50% with c.649dupC mutation) | Benign familial infantile seizures<br>Infantile convulsions with choreoathetosis | The majority of patients respond to carbamazepine.[181] |
| | | Benign paroxysmal torticollis[176]<br>Hemiplegic migraine[177,178] | Some patients may not require/choose treatment. |
| | | Episodic ataxia[179] | Frequency of episodes may diminish with age. |
| | | Acute ataxia[180] | For those with carbamazepine sensitivity, topiramate[182] or other anticonvulsants can be beneficial. |
| Paroxysmal nonkinesigenic dyskinesia | PNKD (MR-1 or PNKD) | Oculogyric crises<br>Blepharospasm | Benzodiazepines: diazepam, clonazepam<br>(>90% may have a good initial response that may reduce with time[170])<br>GPi DBS[183,184] |
| | KCNMA1[185,186] | Developmental delay<br>Epilepsy | No single agent reported to be consistently beneficial. Benzodiazepines useful in some cases for symptom control |
| | ADCY5[b187] | Sleep-related dyskinesia<br>Facial myokymia<br>Chorea<br>Dystonia<br>Myoclonus dystonia | No single agent reported to be consistently beneficial. Tetrabenazine useful in some cases for partial symptom control.[188] Acetazolamide and other medications trialed with variable benefit.[189] |
| Alternating hemiplegia of childhood | ATP1A3 | Rapid-onset dystonia parkinsonism<br>CAPOS syndrome | Flunarizine[190-192] |
| | SLC2A1(GLUT1)[b193] | Alternating hemiplegia<br>Hemiplegic migraine<br>Infantile epilepsy<br>Epilepsy | Ketogenic diet |
| Paroxysmal exercise-induced dystonia/dyskinesia | SLC2A1 (GLUT1) | SLC2A1<br>Alternating hemiplegia<br>Hemiplegic migraine<br>Infantile epilepsy<br>Epilepsy | Ketogenic diet<br>Triheptanoin[32] Acetazolamide |
| | GCH1[b172] | Spastic paraparesis<br>Typical Segawa disease phenotype | L-dopa |
| | Pyruvate dehydrogenase deficiency (PDHA1) [b194] | | Ketogenic diet, thiamine |
| | PARKIN[b171] | Early-onset parkinsonism | L-dopa |
| | PNKD[b] (after prolonged exercise)[195] | Paroxysmal nonkinesigenic dyskinesia | Benzodiazepines |
| Episodic ataxia (EA)[a] | EA1 (KCNA1) | Myokymia (classically associated with EA1) | Carbamazepine, valproate, acetazolamide |
| | EA2 (CACNA1A) | Benign paroxysmal torticollis and paroxysmal tonic upgaze of infancy (classically associated with EA2) | Acetazolamide |

[a]Phenotype associated with various genes.
[b]Variation from typical phenotype for this gene.
CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss.

suggested a trend in improvement of dystonia or tics, the review found that studies to date were either underpowered or not designed to examine movement disorder improvement as a primary outcome. The biological basis of cannabinoid use in movement disorders is outlined in a recent review,[156] but better designed clinical studies will be required to examine their role further, particularly in children.

### Botulinum Toxin A

The botulinum toxins are naturally occurring toxins produced by *Clostridium botulinum*. The main serotype used in clinical practice is botulinum toxin A (BoNT-A). BoNT-A cleaves neuronal SNAP 25 protein required for fusion of acetylcholine-containing vesicles to the axonal cell membrane at motor end plates. Although BoNT-A is effective in the treatment of spasticity associated with CP,[157,158] an evidence base to support its use in dystonia is not well established.[119] BoNT-A is injected intramuscularly into targeted muscles, at intervals of 3 months or more. In children, injections are typically performed using sedation and/or general anaesthetic. Children with severe CP,[159] particularly those with impaired swallow,[160] may be at increased risk of adverse events following BoNT-A.

### Other Medications

Some other medications of note that are used for movement disorder management include beta blockers such as propranolol for tremor,[161,162] amantadine for L-dopa-induced dyskinesia[163] or drug-induced parkinsonism,[99] and tizanidine for muscle relaxation in severe dystonia often in those with mixed spasticity as in CP.[164] Though mainly used for tremor, beta blockers have some effects on the catecholamine effects of stress, which can be relevant in some patients with tremor. Beta blockers should be avoided in asthmatic children.

### Management of Status Dystonicus

We have not addressed a detailed management of status dystonicus, but have discussed agents that may assist in management of severe movement disorder exacerbations such as in GNAO1-related disorders and anti-NMDAR encephalitis. Proposed treatment pathways are outlined in recent reviews.[97,165] Reversal of the underlying cause is a key aspect of management in addition to symptomatic treatment. Sometimes, the cause may be therapy related, such as sudden interruption of DBS, intrathecal baclofen, or other medications. For symptomatic management, we find sedative agents, particularly oral clonidine, at frequent and high doses as a valuable tool for children with severe movement disorder exacerbations. Emergent DBS can be useful[166-169] and life-saving,[170] as exemplified by several reports of GNAO1-related movement disorders,[123] but is limited by availability around the world.

### Treatment of Paroxysmal Movement Disorders

Paroxysmal movement disorders have classically been grouped according to their precipitating trigger such as movement or exercise (Table 4). The underlying genetic determinants of these disorders are now better understood with the discovery of gene associations such as *PRRT2* with paroxysmal kinesigenic dyskinesia, though a proportion of patients still remain unexplained. A recent cohort study[171] and reviews[172,173] summarize the spectrum of these disorders, genetic associations, and phenotypic pleiotropy of the paroxysmal disorders, such as exercise-induced dystonia observed in both GLUT1 deficiency as well as GTP cyclohydrolase deficiency.[174] There is also therapeutic pleiotropy in these disorders, for example, acetazolamide may be useful for episodic ataxia type 2, but can also benefit alternating hemiplegia[175] or GLUT1-deficiency–related movement disorders.[176,177]

## Neuromodulation

Neuromodulation is a term used for various interventions that may include targeted electrical, magnetic, or chemical stimulation to alter neurological function. Such techniques include noninvasive transcutaneous electrical neurostimulation, transcranial magnetic stimulation (TMS), direct current transcranial stimulation, invasive spinal neuromodulation, cochlear implantation, DBS, intrathecal baclofen (ITB), and vagal nerve stimulation. Various neuromodulation techniques in children and their current status were recently summarized.[198] We restrict discussion to those techniques that are in current clinical use or trials for movement disorders in children.

DBS has been demonstrated to benefit dystonia in adults and children.[199] Comparative studies in children are lacking, but there is accumulating evidence from open label studies to help patient selection and guide the provision of DBS to children with monogenic disorders and secondary dystonia syndromes such as CP.[200] Despite the existence of a newer classification system for dystonia,[201] several national therapeutic administration bodies such as the U.S. Food and Drug Administration still utilize the previous terminology of primary and secondary dystonia with regards to use of DBS. The currently understood role of DBS in selected childhood-onset movement disorder syndromes is summarized in Table 5. Overall, the role of DBS can be summarized from literatures as below:

- DBS is beneficial in children and adults with primary dystonia such as DYT1.[202] Genetic etiology is likely to influence expected benefit from DBS.[203,204]
- The benefit from DBS is likely to be more the less the duration of life lived with dystonia.[205,206]
- DBS can benefit children with dystonia attributed to progressive disorders like PKAN[207-209] or with dystonia associated with brain injury (hypoxia- or kernicterus-related CP),[200,210] though the magnitude of motor effects measured by conventional scales is less compared to primary dystonia, and benefit reported is variable.

DBS has been trialed in the treatment of movement disorders associated with other rare disorders, such

**TABLE 5.** The role and evidence for DBS in selected childhood-onset movement disorders

| Disorder Category | Underlying Disorder (Gene) | Progressive | Role and Evidence for DBS |
|---|---|---|---|
| Monogenic disorders | ADCY5-associated movement disorder | – | Partial benefit from GPi DBS in some patients[208-210] |
| | DYT6 (THAP1) | – | DBS is partially effective (~30% improvement) in some patients (~60%)[211,212] |
| | DYT1 (TOR1A) | +/– | GPi DBS is effective for dystonia in ~90% of patients, response can diminish with time, and degree of benefit can vary from 50% upward.[200,211,212] |
| | DYT11 (SGCE) | +/– | GPi DBS is effective for dystonia in most patients, with 50% or more benefit, though myoclonus may respond less consistently.[211,213,214] |
| | | | Some patients may benefit from VIM DBS.[211,215] |
| | DYT28 (KMT2B) | +/– | GPi DBS is effective for dystonia.[216] |
| | GNAO1-associated movement disorder | +/– | DBS is effective for hyperkinetic movement disorder and can be life-saving.[93,122,217-220] |
| | Rapid-onset dystonia parkinsonism (ATP1A3) | +/– | GPi DBS is ineffective and risk of worsening in some patients.[221-223] |
| | X-linked dystonia parkinsonism–Lubag syndrome (TAF1) | + | GPi DBS is effective for dystonia and can be life-saving.[224,225] |
| | Pantothenate kinase-associated neurodegeneration (PANK2) | + | GPi DBS can lead to substantial benefit and stabilization of disease course in patients with milder phenotype.[226-228] |
| | | | Variable response to GPi DBS in patients with early-onset progressive disease. This is not reported to persist beyond few months.[229] |
| | | | Potential role of STN DBS in temporary stabilization of disease course[230] |
| Secondary dystonia syndromes | Dystonic cerebral palsy | – | Variable benefits described with GPi DBS. The magnitude of benefit is less than in primary dystonia syndromes.[231,232] |
| | Tardive dystonia | +/– | GPi DBS is effective for dystonia[233-236] |

+ = progressive disease course in most patients with disorder; – = nonprogressive disease course in most patients with disorder; +/– = may be progressive in some patients with disorder.
GPi, globus pallidus interna; VIM, ventralis intermediate nucleus of the thalamus.

as Wilson's disease, ataxia telangiectasia, chorea acanthocytosis, juvenile Huntington's disease, and benign hereditary chorea, but the benefits described are inconsistent and case reports are too few to draw robust conclusions. DBS has also been trialed for Tourette's disorder, as recently reviewed,[240] and various surgical targets are described with the medial thalamus being most commonly reported. Benefits described in Tourette's disorder are variable and may not be sustained. In view of the natural history of reduction in tic severity over time and the relatively higher impact from psychiatric comorbidity to functional impairment, we would recommend caution with premature consideration of DBS for children, including teenagers, with tic disorders.

## Other Neuromodulation Techniques for Treatment of Movement Disorders

ITB pump systems enable delivery of baclofen to GABA receptors in the dorsal spinal cord bypassing the blood–brain barrier. This allows significantly reduced doses (usually 500–1,000 μg/day)[241] than oral baclofen and reduces systemic side effects of the drug. ITB is typically used in nonambulatory children with severe generalized hypertonia, usually in children with CP who may have either predominant spasticity, dystonia, or both. Studies have suggested ITB as effective in reducing dystonia[119] and spasticity,[242] at least in the short term, and shown to be provide benefits to comfort and quality of life.[242] Adverse events related to device malfunction, infections, as well as availability and the requirement for regular pump refills may limit its use.

Lesioning of targets, such as the pallidum and thalamus, has been utilized for movement disorder management for several years. Recent use has declined in many settings with availability of DBS, because lesioning, in contrast to DBS, is irreversible. Bilateral lesioning also has more associated motor morbidity. Lesioning may still have a role in some situations where the surgical target may already be atrophic or injured such as in kernicterus or neurometabolic disorders with pallidal atrophy. Lesioning is also an option in resource-poor settings or in settings where it may be risky to undertake invasive surgery, for example in children with immunodeficiency or those who may not be able or

willing to attend regular follow-up.[243] Other situations where lesioning may be utilized is after failure of DBS or a DBS-related complication that precludes reimplantation. Focused ultrasound, although also producing a lesioning affect, has the advantages of being less invasive and more precise, and is currently used mainly for some adult patients with movement disorders, particularly essential tremor.[244,245] Ultrasound may be suitable for patients who have significant comorbidity and are a surgical risk, but is limited by expertise and equipment availability as well as lack of experience in application to children.

TMS is currently utilized in clinical practice to aid neurophysiological studies, such as measurement of central motor conduction times.[246] Repetitive TMS (rTMS) techniques have been shown to be safe in children.[247] rTMS has been shown to produced noticeable neurological benefit in poststroke patients, including children with perinatal or neonatal stroke.[248] The magnitude of effects noted may vary, but the main challenges are immobility of equipment and the requirement for sustained repetitive stimulation to maintain benefits.

## Prevention of Secondary Complications and Physical Therapies

The disability associated with childhood movement disorders may also be influenced by associated motor problems, particularly when the movement disorder has been present lifelong. "Negative signs," such as weakness, ataxia, reduced selective motor control, and developmental dyspraxia, are commonly noted, but can be difficult to assess in the presence of a movement disorder.[249] However, targeted treatment of these motor problems can be valuable where the focus of the intervention is on associated disability. Physical therapies, such as physiotherapy and occupational therapy, supported by the use of orthotics, splints, and assistive technologies, comprise the predominant approach to treatment. Physical therapies typically use performance-based and goal-directed approaches to support motor learning around a specific task of interest. There is evidence for the efficacy of such approaches using various techniques and settings (e.g., constraint-induced movement therapy, occupational therapy after botulinum toxin, and gait training[250,251]). Orthotics and splints, made from rigid or semirigid materials, can provide support for individual or multiple joints to assist function (e.g., walking) where weakness or hypertonia is present. Weighted garments may be used in tremor. Dynamic orthotic suits, typically made of lycra or similar fabric, may also be used for whole-body segments, but their utility is unclear.[252]

## Musculoskeletal Deformities

Children with movement disorders may develop musculoskeletal deformities, particularly where the movement disorder has been present from birth or early in life. Muscle and tendon contracture may limit range of movement across a joint and contribute to disability, and torsional bony deformities may impair movement through lever arm dysfunction. Scoliosis[253] and hip-joint subluxation[254] are common in more-severe forms of CP and may cause pain and have significant impact on health-related quality of life. Milder contractures may be treated by stretch interventions such as splinting or serial casting. If these methods fail, surgical intramuscular or tendon lengthening may be required, and bony deformities require orthopedic approaches.

## Psychiatric and Intellectual Comorbidity

It has been recognized for decades that patients with movement disorders have increased psychiatric comorbidity, and indeed psychiatric features may predate the movement phenomenon in patients with Huntington's disease, Wilson's disease, or Niemann-Pick disease type C. The psychiatric comorbidity is best described for patients with Tourette's syndrome, and it is accepted that pure Tourette's without comorbidity is the exception, with only 15% of Tourette's patients having no comorbidity.[255] ADHD, obsessive-compulsive disorder (OCD), and other emotional and psychiatric features are common and potentially impairing. By contrast, literature on other non-Tourette's movement disorders for psychiatric comorbidity is scarce, although recent review suggests psychiatric comorbidity is also high in dystonia[256] and stereotypies.[257] Defining and treating the psychiatric comorbidity may be more important than treating the associated movement disorder.[258-260] Clonidine or guanfacine are partially effective for both tics and ADHD and can help sleep induction and reduce anxiety. Stimulants are the best treatment of ADHD, and recent studies clearly show they are effective for treating ADHD in children with tics.[258,259,261] Families need to be counseled that, in some children, the tics may be exacerbated by stimulants; often this is transient, and indeed large studies have shown that stimulants actually reduce tics in the cohort setting. Combinations of clonidine or guanfacine and stimulants can be more effective than single agents alone, if the ADHD is impairing. Likewise, treating emotional symptoms can be a therapeutic priority and also result in improved function of the child and quality of life. In addition to psychological therapies, serotonin reuptake inhibitors (SSRIs) or other psychotropic drugs may be useful. Fluoxetine and sertraline have the best evidence

of effect and safety in children, although they can be activating in some children, and other SSRIs or other antidepressants can be considered subject to safety discussions.

## Conclusion

We have summarized an approach to therapeutic considerations in children with movement disorders attributed to various etiologies. The overarching themes are treating underlying reversible or modifiable disorders and considering what symptom is most functionally limiting for the child. We are in an era of rapid advances in genomic discovery and genetic interventions, as well as emerging roles of neuromodulation techniques, which we have highlighted with contemporary references with regard to childhood movement disorders.

## References


1. Cusick A, McIntyre S, Novak I, Lannin N, Lowe K. A comparison of goal attainment scaling and the Canadian Occupational Performance Measure for paediatric rehabilitation research. Pediatr Rehabil 2006;9:149–157.
2. World Health Organization. International Classification of Functioning, Disability, and Health: Children and Youth Version: ICF-CY. Geneva, Switzerland: World Health Organization; 2007.
3. Brunklaus A, Pohl K, Zuberi SM, de Sousa C. Investigating neuroblastoma in childhood opsoclonus-myoclonus syndrome. Arch Dis Child 2012;97:461–463.
4. Mitchell WG, Wooten AA, O'Neil SH, Rodriguez JG, Cruz RE, Wittern R. Effect of increased immunosuppression on developmental outcome of opsoclonus myoclonus syndrome (OMS). J Child Neurol 2015;30:976–982.
5. Pranzatelli MR, Tate ED. Trends and tenets in relapsing and progressive opsoclonus-myoclonus syndrome. Brain Dev 2016;38:439–448.
6. Leuzzi V, Mastrangelo M, Giannini MT, Carbonetti R, Hoffmann GF. Neuromotor and cognitive outcomes of early treatment in tyrosine hydroxylase deficiency type B. Neurology 2017;88:501–502.
7. Ebrahimi-Fakhari D, Van Karnebeek C, Münchau A. Movement disorders in treatable inborn errors of metabolism. Mov Disord 2018 Dec 17. doi: https://doi.org/10.1002/mds.27568. [Epub ahead of print]
8. Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders—clinical advances and future perspectives. Nat Rev Neurol 2015;11:567–584.
9. Kurian MA, Dale RC. Movement disorders presenting in childhood. Continuum (Minneap Minn) 2016;22(4 Movement Disorders):1159–1185.
10. Brennenstuhl H, Jung-Klawitter S, Assmann B, Opladen T. Inherited disorders of neurotransmitters: classification and practical approaches for diagnosis and treatment. neuropediatrics 2019;50:2–14.
11. Jinnah HA, Albanese A, Bhatia KP, et al. Treatable inherited rare movement disorders. Mov Disord 2018;33:21–35.
12. van Karnebeek CD, Houben RF, Lafek M, Giannasi W, Stockler S. The treatable intellectual disability APP www.treatable-id.org: a digital tool to enhance diagnosis & care for rare diseases. Orphanet J Rare Dis 2012;7:47.
13. Leach EL, Shevell M, Bowden K, Stockler-Ipsiroglu S, van Karnebeek CD. Treatable inborn errors of metabolism presenting as cerebral palsy mimics: systematic literature review. Orphanet J Rare Dis 2014;9:197.
14. Zschocke J, Hoffmann GF. Vademecum Metabolicum: Diagnosis and Treatment of Inborn Errors of Metabolism. Stuttgart, Germany: Schattauer Verlag; 2011.
15. Boy N, Muhlhausen C, Maier EM, et al. Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: second revision. J Inherit Metab Dis 2017;40:75–101.
16. Wilcken B. Therapeutic targets in homocystinuria due to cystathionine β-synthase deficiency: new European guidelines. Exp Opin Orphan Drugs 2017;5:1–3.
17. Camacho J, Rioseco-Camacho N. Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. GeneReviews®. Seattle, WA: University of Washington; 2012.
18. Frazier DM, Allgeier C, Homer C, et al. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab 2014;112:210–217.
19. [No authors listed]. [L-dopa-induced movement disorders in Parkinson disease. Amantadine improves dyskinesia]. [Article in German]. MMW Fortschr Med 2001;143(Suppl 2):93.
20. van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis 2017;12:162.
21. Baumgartner MR, Horster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis 2014;9:130.
22. Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet 2015;386:1955–1963.
23. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: a comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis 2014;9:179.
24. Stockler-Ipsiroglu S, van Karnebeek C, Longo N, et al. Guanidinoacetate methyltransferase (GAMT) deficiency: outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring. Mol Genet Metab 2014;111:16–25.
25. Sofou K, Dahlin M, Hallbook T, Lindefeldt M, Viggedal G, Darin N. Ketogenic diet in pyruvate dehydrogenase complex deficiency: short- and long-term outcomes. J Inherit Metab Dis 2017;40:237–245.
26. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. Int J Mol Sci 2017;18:E441.
27. Pineda M, Walterfang M, Patterson MC. Miglustat in Niemann-Pick disease type C patients: a review. Orphanet J Rare Dis 2018;13:140.
28. Brewer GJ, Askari F, Lorincz MT, et al. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. Arch Neurol 2006;63:521–527.
29. Aggarwal A, Bhatt M. Advances in treatment of Wilson disease. Tremor Other Hyperkinet Mov (N Y) 2018;8:525.
30. Wassenberg T, Molero-Luis M, Jeltsch K, et al. Consensus guideline for the diagnosis and treatment of aromatic L-amino acid decarboxylase (AADC) deficiency. Orphanet J Rare Dis 2017;12:12.
31. Kurian MA. SLC6A3-related dopamine transporter deficiency syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. GeneReviews®. Seattle, WA: University of Washington; 1993.
32. Kass HR, Winesett SP, Bessone SK, Turner Z, Kossoff EH. Use of dietary therapies amongst patients with GLUT1 deficiency syndrome. Seizure 2016;35:83–87.

33. Mochel F, Hainque E, Gras D, et al. Triheptanoin dramatically reduces paroxysmal motor disorder in patients with GLUT1 deficiency. J Neurol Neurosurg Psychiatry 2016;87:550–553.

34. Pearl PL, Wiwattanadittakul N, Roullet JB, Gibson KM. Succinic semialdehyde dehydrogenase deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. GeneReviews®. Seattle, WA: University of Washington; 2016.

35. Furukawa Y, Kish S. Tyrosine hydroxylase deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. GeneReviews®. Seattle, WA: University of Washington; 2017.

36. Rilstone JJ, Alkhater RA, Minassian BA. Brain dopamine-serotonin vesicular transport disease and its treatment. N Engl J Med 2013; 368:543–550.

37. Wolf B. Biotinidase deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. GeneReviews®. Seattle, WA: University of Washington; 2016.

38. Ortigoza-Escobar JD, Molero-Luis M, Arias A, et al. Treatment of genetic defects of thiamine transport and metabolism. Expert Rev Neurother 2016;16:755–763.

39. Pranzatelli MR, Tate ED, McGee NR. Demographic, clinical, and immunologic features of 389 children with opsoclonus-myoclonus syndrome: a cross-sectional study. Front Neurol 2017;8:468.

40. Byrne S, Walsh C, Hacohen Y, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. Neurol Neuroimmunol Neuroinflamm 2015;2:e130.

41. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother 2015;15:1391–1419.

42. Dale RC, Merheb V, Pillai S, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain 2012;135(Pt 11):3453–3468.

43. Pawela C, Brunsdon RK, Williams TA, Porter M, Dale RC, Mohammad SS. The neuropsychological profile of children with basal ganglia encephalitis: a case series. Dev Med Child Neurol 2017;59:445–448.

44. Cardoso F, Eduardo C, Silva AP, Mota CC. Chorea in fifty consecutive patients with rheumatic fever. Mov Disord 1997;12:701–703.

45. Moreira J, Kummer A, Harsanyi E, Cardoso F, Teixeira AL. Psychiatric disorders in persistent and remitted Sydenham's chorea. Parkinsonism Relat Disord 2014;20:233–236.

46. Walker K, Brink A, Lawrenson J, Mathiassen W, Wilmshurst JM. Treatment of sydenham chorea with intravenous immunoglobulin. J Child Neurol 2012;27:147–155.

47. Dean SL, Singer HS. Treatment of Sydenham's chorea: a review of the current evidence. Tremor Other Hyperkinet Mov (N Y) 2017; 7:456.

48. Pranzatelli MR, Tate ED, Galvan I, Wheeler A. Controlled pilot study of piracetam for pediatric opsoclonus-myoclonus. Clin Neuropharmacol 2001;24:352–357.

49. Mohammad SS, Fung VS, Grattan-Smith P, et al. Movement disorders in children with anti-NMDAR encephalitis and other autoimmune encephalopathies. Mov Disord 2014;29:1539–1542.

50. Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord 2013;28:543–547.

51. Mohammad SS, Jones H, Hong M, et al. Symptomatic treatment of children with anti-NMDAR encephalitis. Dev Med Child Neurol 2016;58:376–384.

52. Tumas V, Caldas CT, Santos AC, Nobre A, Fernandes RM. Sydenham's chorea: clinical observations from a Brazilian movement disorder clinic. Parkinsonism Relat Disord 2007;13:276–283.

53. Pearce KF, Hildebrandt M, Greinix H, et al. Regulation of advanced therapy medicinal products in Europe and the role of academia. Cytotherapy 2014;16:289–297.

54. Levin AA. Treating disease at the RNA level with oligonucleotides. N Engl J Med 2019;380:57–70.

55. Chien YH, Lee NC, Tseng SH, et al. Efficacy and safety of AAV2 gene therapy in children with aromatic L-amino acid decarboxylase deficiency: an open-label, phase 1/2 trial. Lancet Child Adolesc Health 2017;1:265–273.

56. Rice GI, Meyzer C, Bouazza N, et al. Reverse-transcriptase inhibitors in the Aicardi-Goutieres syndrome. N Engl J Med 2018;379: 2275–2277.

57. Ginn SL, Amaya AK, Alexander IE, Edelstein M, Abedi MR. Gene therapy clinical trials worldwide to 2017: an update. J Gene Med 2018;20:e3015.

58. World Health Organization. International Clinical Trials Registry Platform (ICTRP). http://www.who.int/ictrp/en/ 2010. Accessed January 26, 2019.

59. US National Library of Medicine. Clinical Trials Website. https://clinicaltrials.gov. Accessed January 26, 2019.

60. Crow YJ, Chase DS, Lowenstein Schmidt J, et al. Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. Am J Med Genet A 2015;167A:296–312.

61. Crow YJ, Zaki MS, Abdel-Hamid MS, et al. Mutations in ADAR1, IFIH1, and RNASEH2B presenting as spastic paraplegia. Neuropediatrics 2014;45:386–393.

62. Kothur K, Bandodkar S, Chu S, et al. An open-label trial of JAK 1/2 blockade in progressive IFIH1-associated neuroinflammation. Neurology 2018;90:289–291.

63. Gatti R, Ataxia-telangiectasia. In: Pagon R, Adam M, Ardinger H, eds. GeneReviews®. Seattle, WA: University of Washington; 1999.

64. Chessa L, Leuzzi V, Plebani A, et al. Intra-erythrocyte infusion of dexamethasone reduces neurological symptoms in ataxia teleangiectasia patients: results of a phase 2 trial. Orphanet J Rare Dis 2014;9:5.

65. Ronzitti G, Bortolussi G, van Dijk R, et al. A translationally optimized AAV-UGT1A1 vector drives safe and long-lasting correction of Crigler-Najjar syndrome. Mol Ther Methods Clin Dev 2016;3: 16049.

66. Mink JW, Augustine EF, Adams HR, Marshall FJ, Kwon JM. Classification and natural history of the neuronal ceroid lipofuscinoses. J Child Neurol 2013;28:1101–1105.

67. Geraets RD, Koh S, Hastings ML, Kielian T, Pearce DA, Weimer JM. Moving towards effective therapeutic strategies for neuronal ceroid lipofuscinosis. Orphanet J Rare Dis 2016;11:40.

68. Mole SE, Anderson G, Band HA, et al. Clinical challenges and future therapeutic approaches for neuronal ceroid lipofuscinosis. Lancet Neurol 2019;18:107–116.

69. Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA 2010;303:1929–1937.

70. Sukhodolsky DG, Woods DW, Piacentini J, et al. Moderators and predictors of response to behavior therapy for tics in Tourette syndrome. Neurology 2017;88:1029–1036.

71. Jakubovski E, Reichert C, Karch A, Buddensiek N, Breuer D, Muller-Vahl K. The ONLINE-TICS Study Protocol: a randomized observer-blind clinical trial to demonstrate the efficacy and safety of internet-delivered behavioral treatment for adults with chronic tic disorders. Front Psychiatry 2016;7:119.

72. Koy A, Lin JP, Sanger TD, Marks WA, Mink JW, Timmermann L. Advances in management of movement disorders in children. Lancet Neurol 2016;15:719–735.

73. Tassin J, Durr A, Bonnet AM, et al. Levodopa-responsive dystonia. GTP cyclohydrolase I or parkin mutations? Brain 2000;123(Pt 6): 1112–1121.

74. Straniero L, Guella I, Cilia R, et al. DNAJC12 and dopa-responsive nonprogressive parkinsonism. Ann Neurol 2017;82:640–646.

75. Anikster Y, Haack TB, Vilboux T, et al. Biallelic mutations in DNAJC12 cause hyperphenylalaninemia, dystonia, and intellectual disability. Am J Hum Genet 2017;100:257-266.

76. Paviour DC, Surtees RA, Lees AJ. Diagnostic considerations in juvenile parkinsonism. Mov Disord 2004;19:123-135.

77. Lee WW, Jeon B, Kim R. Expanding the spectrum of dopa-responsive dystonia (DRD) and proposal for new definition: DRD, DRD-plus, and DRD look-alike. J Korean Med Sci 2018;33:e184.

78. Charlesworth G, Mohire MD, Schneider SA, Stamelou M, Wood NW, Bhatia KP. Ataxia telangiectasia presenting as dopa-responsive cervical dystonia. Neurology 2013;81:1148–1151.

79. Annesi G, Savettieri G, Pugliese P, et al. DJ-1 mutations and parkinsonism-dementia-amyotrophic lateral sclerosis complex. Ann Neurol 2005;58:803–807.

80. Paisan-Ruiz C, Guevara R, Federoff M, et al. Early-onset L-dopa-responsive parkinsonism with pyramidal signs due to ATP13A2, PLA2G6, FBXO7 and spatacsin mutations. Mov Disord 2010;25: 1791–1800.

81. Paviour DC, Revesz T, Holton JL, Evans A, Olsson JE, Lees AJ. Neuronal intranuclear inclusion disease: report on a case originally diagnosed as dopa-responsive dystonia with Lewy bodies. Mov Disord 2005;20:1345–1349.

82. Albanese A, Valente EM, Romito LM, Bellacchio E, Elia AE, Dallapiccola B. The PINK1 phenotype can be indistinguishable from idiopathic Parkinson disease. Neurology 2005;64: 1958–1960.

83. Ebrahimi-Fakhari D, Maas B, Haneke C, et al. Disruption of SOX6 is associated with a rapid-onset dopa-responsive movement disorder, delayed development, and dysmorphic features. Pediatr Neurol 2015;52:115–118.

84. Vanderver A, Tonduti D, Auerbach S, et al. Neurotransmitter abnormalities and response to supplementation in SPG11. Mol Genet Metab 2012;107:229–233.

85. Guidubaldi A, Piano C, Santorelli FM, et al. Novel mutations in SPG11 cause hereditary spastic paraplegia associated with early-onset levodopa-responsive Parkinsonism. Mov Disord 2011;26: 553–556.

86. Anheim M, Lagier-Tourenne C, Stevanin G, et al. SPG11 spastic paraplegia. A new cause of juvenile parkinsonism. J Neurol 2009; 256:104–108.

87. Masson R, Pagliano E, Baranello G. Efficacy of oral pharmacological treatments in dyskinetic cerebral palsy: a systematic review. Dev Med Child Neurol 2017;59:1237–1248.

88. Lumsden DE, Kaminska M, Tomlin S, Lin JP. Medication use in childhood dystonia. Eur J Paediatr Neurol 2016;20:625–629.

89. Visser JE, Schretlen DJ, Bloem BR, Jinnah HA. Levodopa is not a useful treatment for Lesch-Nyhan disease. Mov Disord 2011;26: 746–749.

90. Cloud LJ, Jinnah HA. Treatment strategies for dystonia. Expert Opin Pharmacother 2010;11:5–15.

91. Malek N, Fletcher N, Newman E. Diagnosing dopamine-responsive dystonias. Pract Neurol 2015;15:340–345.

92. Porta F, Mussa A, Concolino D, Spada M, Ponzone A. Dopamine agonists in 6-pyruvoyl tetrahydropterin synthase deficiency. Neurology 2009;73:633–637.

93. Kurian MA, Li Y, Zhen J, et al. Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: an observational cohort and experimental study. Lancet Neurol 2011; 10:54–62.

94. Danti FR, Galosi S, Romani M, et al. GNAO1 encephalopathy: broadening the phenotype and evaluating treatment and outcome. Neurol Genet 2017;3:e143.

95. Solmi M, Pigato G, Kane JM, Correll CU. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. Drug Des Devel Ther 2018;12:1215–1238.

96. Manji H, Howard RS, Miller DH, et al. Status dystonicus: the syndrome and its management. Brain 1998;121(Pt 2):243–252.

97. Grosso S, Verrotti A, Messina M, Sacchini M, Balestri P. Management of status dystonicus in children. Cases report and review. Eur J Paediatr Neurol 2012;16:390–395.

98. Jankovic J, Jimenez-Shahed J, Budman C, et al. Deutetrabenazine in tics associated with Tourette syndrome. Tremor Other Hyperkinet Mov (N Y) 2016;6:422.

99. Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. Expert Opin Pharmacother 2016;17: 2461–2470.

100. Gaffney GR, Perry PJ, Lund BC, Bever-Stille KA, Arndt S, Kuperman S. Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 2002;41:330–336.

101. Gerasch S, Kanaan AS, Jakubovski E, Muller-Vahl KR. Aripiprazole improves associated comorbid conditions in addition to tics in adult patients with Gilles de la Tourette syndrome. Front Neurosci 2016;10:416.

102. Huys D, Hardenacke K, Poppe P, Bartsch C, Baskin B, Kuhn J. Update on the role of antipsychotics in the treatment of Tourette syndrome. Neuropsychiatr Dis Treat 2012;8:95–104.

103. Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 2: treatment of tardive dyskinesia. Drugs 2016;76:779–787.

104. Tchan MC, Sillence D. Extrapyramidal symptoms and medication use in Mucopolysaccharidosis type III. J Intellect Dev Disabil 2009; 34:275–279.

105. Zai CC, Maes MS, Tiwari AK, Zai GC, Remington G, Kennedy JL. Genetics of tardive dyskinesia: promising leads and ways forward. J Neurol Sci 2018;389:28–34.

106. Burke RE, Fahn S, Marsden CD. Torsion dystonia: a double-blind, prospective trial of high-dosage trihexyphenidyl. Neurology 1986; 36:160–164.

107. Rice J, Waugh MC. Pilot study on trihexyphenidyl in the treatment of dystonia in children with cerebral palsy. J Child Neurol 2009; 24:176–182.

108. Lorber J. A controlled investigation of artane in cerebral palsy. Arch Dis Child 1955;30:251–253.

109. Ben-Pazi H. Trihexyphenidyl improves motor function in children with dystonic cerebral palsy: a retrospective analysis. J Child Neurol 2011;26:810–816.

110. Pisani A, Bernardi G, Ding J, Surmeier DJ. Re-emergence of striatal cholinergic interneurons in movement disorders. Trends Neurosci 2007;30:545–553.

111. Deffains M, Bergman H. Striatal cholinergic interneurons and cortico-striatal synaptic plasticity in health and disease. Mov Disord 2015;30:1014–1025.

112. Ozelius L, Lubarr N. DYT1 early-onset isolated dystonia. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. SourceGeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2019.

113. Dijk JM, Tijssen MA. Management of patients with myoclonus: available therapies and the need for an evidence-based approach. Lancet Neurol 2010;9:1028–1036.

114. Fahn S. High-dosage anticholinergic therapy in dystonia. Adv Neurol 1983;37:177–188.

115. Bergman H, Soares-Weiser K. Anticholinergic medication for antipsychotic-induced tardive dyskinesia. Cochrane Database Syst Rev 2018;1:CD000204.

116. Tammenmaa IA, Sailas E, McGrath JJ, Soares-Weiser K, Wahlbeck K. Systematic review of cholinergic drugs for neuroleptic-induced tardive dyskinesia: a meta-analysis of randomized controlled trials. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:1099–1107.

117. Sanger TD, Bastian A, Brunstrom J, et al. Prospective open-label clinical trial of trihexyphenidyl in children with secondary dystonia due to cerebral palsy. J Child Neurol 2007;22:530–537.

118. Whelan MA, Delgado MR. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2010;75:669.

119. Fehlings D, Brown L, Harvey A, et al. Pharmacological and neurosurgical interventions for managing dystonia in cerebral palsy: a systematic review. Dev Med Child Neurol 2018;60:356–366.

120. Lin CC, Hung YY, Tsai MC, Huang TL. The lorazepam and diazepam protocol for catatonia due to general medical condition and substance in liaison psychiatry. PLoS One 2017;12:e0170452.

121. Nakou V, Williamson K, Arichi T, et al. Safety and efficacy of high-dose enteral, intravenous, and transdermal clonidine for the acute management of severe intractable childhood dystonia and status dystonicus: an illustrative case-series. Eur J Paediatr Neurol 2017;21:823–832.

122. Sayer C, Lumsden DE, Kaminska M, Lin JP. Clonidine use in the outpatient management of severe secondary dystonia. Eur J Paediatr Neurol 2017;21:621–626.

123. Waak M, Mohammad SS, Coman D, et al. GNAO1-related movement disorder with life-threatening exacerbations: movement phenomenology and response to DBS. J Neurol Neurosurg Psychiatry 2018;89:221–222.

124. Murphy TK, Fernandez TV, Coffey BJ, et al. Extended-release guanfacine does not show a large effect on tic severity in children with chronic tic disorders. J Child Adolesc Psychopharmacol 2017;27:762–770.

125. Boon-yasidhi V, Kim YS, Scahill L. An open-label, prospective study of guanfacine in children with ADHD and tic disorders. J Med Assoc Thai 2005;88(Suppl 8):S156–S162.

126. Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry 2001;158:1067–1074.

127. Dayton D, Kowalczyk AK. Dexmedetomidine suppressed involuntary movement in a patient with cerebral palsy. A A Case Rep 2014;3:40–41.

128. Yamanaka D, Kawano T, Tateiwa H, Iwata H, Locatelli FM, Yokoyama M. Successful management of dexmedetomidine for postoperative intensive care sedation in a patient with anti-NMDA receptor encephalitis: a case report and animal experiment. Springerplus 2016;5:1380.

129. Daoud AS, Zaki M, Shakir R, al-Saleh Q. Effectiveness of sodium valproate in the treatment of Sydenham's chorea. Neurology 1990;40:1140–1141.

130. Genel F, Arslanoglu S, Uran N, Saylan B. Sydenham's chorea: clinical findings and comparison of the efficacies of sodium valproate and carbamazepine regimens. Brain Dev 2002;24:73–76.

131. Pena J, Mora E, Cardozo J, Molina O, Montiel C. Comparison of the efficacy of carbamazepine, haloperidol and valproic acid in the treatment of children with Sydenham's chorea: clinical follow-up of 18 patients. Arq Neuropsiquiatr 2002;60:374–377.

132. Hainque E, Vidailhet M, Cozic N, et al. A randomized, controlled, double-blind, crossover trial of zonisamide in myoclonus-dystonia. Neurology 2016;86:1729–1735.

133. Sakamoto S, Monden Y, Fukai R, et al. A case of severe movement disorder with GNAO1 mutation responsive to topiramate. Brain Dev 2017;39:439–443.

134. Jankovic J, Jimenez-Shahed J, Brown LW. A randomised, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. J Neurol Neurosurg Psychiatry 2010;81:70–73.

135. Sasso E, Perucca E, Fava R, Calzetti S. Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. Clin Neuropharmacol 1990;13:67–76.

136. Goumentouk AD, Hurwitz TA, Zis AP. Primidone in drug-induced tremor. J Clin Psychopharmacol 1989;9:451.

137. Chakrabarti A, Pearce JM. Essential tremor: response to primidone. J Neurol Neurosurg Psychiatry 1981;44:650.

138. Greenblatt HK, Greenblatt DJ. Gabapentin and pregabalin for the treatment of anxiety disorders. Clin Pharmacol Drug Dev 2018;7:228–232.

139. Fornaro M, Maremmani AG, Colicchio MG, et al. A case of severe oral self-injurious Tourette's syndrome alleviated by pregabalin. Gen Hosp Psychiatry 2012;34:321 e.1–e4.

140. Karosin C, Kofler M, Mayr A, Saltuari L. Pregabalin: a treatment option for dystonia? Neurol Sci 2012;33:351–354.

141. Baek WS. Pregabalin resolves refractory aparathyroid paroxysmal kinesigenic choreoathetosis. Clin Neuropharmacol 2012;35:203.

142. Liow NY, Gimeno H, Lumsden DE, et al. Gabapentin can significantly improve dystonia severity and quality of life in children. Eur J Paediatr Neurol 2016;20:100–107.

143. Andrzejewski K, Barbano R, Mink J. Cannabinoids in the treatment of movement disorders: a systematic review of case series and clinical trials. Basal Ganglia 2016;6:173–181.

144. Brunnauer A, Segmiller FM, Volkamer T, Laux G, Muller N, Dehning S. Cannabinoids improve driving ability in a Tourette's patient. Psychiatry Res 2011;190:382.

145. Muller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. Neuropsychopharmacology 2003;28:384–388.

146. Sandyk R, Awerbuch G. Marijuana and Tourette's syndrome. J Clin Psychopharmacol 1988;8:444–445.

147. Chagas MH, Zuardi AW, Tumas V, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol 2014;28:1088–1098.

148. Sieradzan KA, Fox SH, Hill M, Dick JP, Crossman AR, Brotchie JM. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology 2001;57:2108–2111.

149. Jabusch HC, Schneider U, Altenmuller E. Delta9-tetrahydrocannabinol improves motor control in a patient with musician's dystonia. Mov Disord 2004;19:990–991.

150. Gauter B, Rukwied R, Konrad C. Cannabinoid agonists in the treatment of blepharospasm—a case report study. Neuro Endocrinol Lett 2004;25:45–48.

151. Sandyk R, Snider SR, Consroe P, Elias SM. Cannabidiol in dystonic movement disorders. Psychiatry Res 1986;18:291.

152. Uribe Roca MC, Micheli F, Viotti R. Cannabis sativa and dystonia secondary to Wilson's disease. Mov Disord 2005;20:113–115.

153. Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. Ann Neurol 1983;13:669–671.

154. Curtis A, Mitchell I, Patel S, Ives N, Rickards H. A pilot study using nabilone for symptomatic treatment in Huntington's disease. Mov Disord 2009;24:2254–2259.

155. Curtis A, Rickards H. Nabilone could treat chorea and irritability in Huntington's disease. J Neuropsychiatry Clin Neurosci 2006;18:553–554.

156. Peres FF, Lima AC, Hallak JEC, Crippa JA, Silva RH, Abilio VC. Cannabidiol as a promising strategy to treat and prevent movement disorders? Front Pharmacol 2018;9:482.

157. Hoare BJ, Wallen MA, Imms C, Villanueva E, Rawicki HB, Carey L. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). Cochrane Database Syst Rev 2010;(1):CD003469.

158. Copeland L, Edwards P, Thorley M, et al. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. J Pediatr 2014;165:140–146.e4.

159. Naidu K, Smith K, Sheedy M, Adair B, Yu X, Graham HK. Systemic adverse events following botulinum toxin A therapy in children with cerebral palsy. Dev Med Child Neurol 2010;52:139–144.

160. Paget SP, Swinney CM, Burton KLO, Bau K, O'Flaherty SJ. Systemic adverse events after botulinum neurotoxin A injections in children with cerebral palsy. Dev Med Child Neurol 2018;60:1172–1177.

161. Fasano A, Bove F, Lang AE. The treatment of dystonic tremor: a systematic review. J Neurol Neurosurg Psychiatry 2014;85:759–769.

162. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. Lancet Neurol 2011;10:148–161.

163. Perez-Lloret S, Rascol O. Efficacy and safety of amantadine for the treatment of L-DOPA-induced dyskinesia. J Neural Transm (Vienna) 2018;125:1237–1250.

164. Dai AI, Aksoy SN, Demiryurek AT. Comparison of efficacy and side effects of oral baclofen versus tizanidine therapy with adjuvant botulinum toxin type A in children with cerebral palsy and spastic equinus foot deformity. J Child Neurol 2016;31:184–189.

165. Allen NM, Lin JP, Lynch T, King MD. Status dystonicus: a practice guide. Dev Med Child Neurol 2014;56:105–112.

166. Nerrant E, Gonzalez V, Milesi C, et al. Deep brain stimulation treated dystonia-trajectory via status dystonicus. Mov Disord 2018;33:1168–1173.

167. Lobato-Polo J, Ospina-Delgado D, Orrego-Gonzalez E, Gomez-Castro JF, Orozco JL, Enriquez-Marulanda A. Deep brain stimulation surgery for status dystonicus: a single-center experience and literature review. World Neurosurg 2018;114:e992–e1001.

168. Ben-Haim S, Flatow V, Cheung T, Cho C, Tagliati M, Alterman RL. Deep brain stimulation for status dystonicus: a case series and review of the literature. Stereotact Funct Neurosurg 2016;94:207–215.

169. Trezza A, Antonini A, Sganzerla EP, Landi A. Globus pallidus internus deep brain stimulation for the treatment of status dystonicus in tardive dystonia. Acta Neurochir (Wien) 2016;158: 1789–1791.

170. Walcott BP, Nahed BV, Kahle KT, Duhaime AC, Sharma N, Eskandar EN. Deep brain stimulation for medically refractory life-threatening status dystonicus in children. J Neurosurg Pediatr 2012;9:99–102.

171. Erro R, Sheerin UM, Bhatia KP. Paroxysmal dyskinesias revisited: a review of 500 genetically proven cases and a new classification. Mov Disord 2014;29:1108–1116.

172. Silveira-Moriyama L, Kovac S, Kurian MA, et al. Phenotypes, genotypes, and the management of paroxysmal movement disorders. Dev Med Child Neurol 2018;60:559–565.

173. Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. Brain 2015;138(Pt 12):3476–3495.

174. Dale RC, Melchers A, Fung VS, Grattan-Smith P, Houlden H, Earl J. Familial paroxysmal exercise-induced dystonia: atypical presentation of autosomal dominant GTP-cyclohydrolase 1 deficiency. Dev Med Child Neurol 2010;52:583–586.

175. Pisciotta L, Gherzi M, Stagnaro M, et al. Alternating hemiplegia of childhood: pharmacological treatment of 30 Italian patients. Brain Dev 2017;39:521–528.

176. Anheim M, Maillart E, Vuillaumier-Barrot S, et al. Excellent response to acetazolamide in a case of paroxysmal dyskinesias due to GLUT1-deficiency. J Neurol 2011;258:316–317.

177. Chambon R, Vuillaumier-Barrot S, Seta N, Wagner S, Sarret C. Partial effectiveness of acetazolamide in a mild form of GLUT1 deficiency: a pediatric observation. Mov Disord 2013;28: 1749–1751.

178. Dale RC, Gardiner A, Antony J, Houlden H. Familial PRRT2 mutation with heterogeneous paroxysmal disorders including paroxysmal torticollis and hemiplegic migraine. Dev Med Child Neurol 2012;54:958–960.

179. Castiglioni C, Lopez I, Riant F, Bertini E, Terracciano A. PRRT2 mutation causes paroxysmal kinesigenic dyskinesia and hemiplegic migraine in monozygotic twins. Eur J Paediatr Neurol 2013;17: 254–258.

180. Dale RC, Gardiner A, Branson JA, Houlden H. Benefit of carbamazepine in a patient with hemiplegic migraine associated with PRRT2 mutation. Dev Med Child Neurol 2014;56:910.

181. Gardiner AR, Bhatia KP, Stamelou M, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. Neurology 2012;79:2115–2121.

182. Legris N, Chassin O, Nasser G, Riant F, Tournier-Lasserve E, Denier C. Acute-onset ataxia and transient cerebellar diffusion restriction associated with a PRRT2 mutation. J Stroke Cerebrovasc Dis 2019;28:e3–e4.

183. Bruno MK, Hallett M, Gwinn-Hardy K, et al. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. Neurology 2004;63:2280–2287.

184. Huang YG, Chen YC, Du F, et al. Topiramate therapy for paroxysmal kinesigenic choreoathetosis. Mov Disord 2005;20:75–77.

185. van Coller R, Slabbert P, Vaidyanathan J, Schutte C. Successful treatment of disabling paroxysmal nonkinesigenic dyskinesia with deep brain stimulation of the globus pallidus internus. Stereotact Funct Neurosurg 2014;92:388–392.

186. Yamada K, Goto S, Soyama N, et al. Complete suppression of paroxysmal nonkinesigenic dyskinesia by globus pallidus internus pallidal stimulation. Mov Disord 2006;21:576–579.

187. Zhang ZB, Tian MQ, Gao K, Jiang YW, Wu Y. De novo KCNMA1 mutations in children with early-onset paroxysmal dyskinesia and developmental delay. Mov Disord 2015;30: 1290–1292.

188. Du W, Bautista JF, Yang H, et al. Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder. Nat Genet 2005;37:733–738.

189. Friedman JR, Meneret A, Chen DH, et al. ADCY5 mutation carriers display pleiotropic paroxysmal day and nighttime dyskinesias. Mov Disord 2016;31:147–148.

190. Mencacci NE, Erro R, Wiethoff S, et al. ADCY5 mutations are another cause of benign hereditary chorea. Neurology 2015;85: 80–88.

191. Shaw C, Hisama F, Friedman J, Bird TD. ADCY5-related dyskinesia. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. GeneReviews®. Seattle, WA: University of Washington; 1993–2019. 2014 Dec 18 [updated 2015 Dec 17].

192. Aishworiya R, Low PS, Tay SK. Alternating hemiplegia of childhood: successful treatment with topiramate and flunarizine, a case report. Ann Trop Paediatr 2011;31:149–152.

193. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. Neurology 1993;43:36–41.

194. Casaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. Lancet 1984;2:579.

195. Rotstein M, Doran J, Yang H, Ullner PM, Engelstad K, De Vivo DC. Glut1 deficiency and alternating hemiplegia of childhood. Neurology 2009;73:2042–2044.

196. Castiglioni C, Verrigni D, Okuma C, et al. Pyruvate dehydrogenase deficiency presenting as isolated paroxysmal exercise induced dystonia successfully reversed with thiamine supplementation. Case report and mini-review. Eur J Paediatr Neurol 2015;19:497–503.

197. Erro R, Stamelou M, Ganos C, et al. The clinical syndrome of paroxysmal exercise-induced dystonia: diagnostic outcomes and an algorithm. Mov Disord Clin Pract 2014;1:57–61.

198. Lin JP. Advances in neuromodulation in children: current experience and future directions. Eur J Paediatr Neurol 2017;21:1–2.

199. Vidailhet M, Jutras MF, Roze E, Grabli D. Deep brain stimulation for dystonia. Handb Clin Neurol 2013;116:167–187.

200. Koy A, Hellmich M, Pauls KA, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: a meta-analysis. Mov Disord 2013;28:647–654.

201. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013; 28:863–873.

202. Fox MD, Alterman RL. Brain stimulation for torsion dystonia. JAMA Neurol 2015;72:713–719.

203. Elkaim LM, Alotaibi NM, Sigal A, et al. Deep brain stimulation for pediatric dystonia: a meta-analysis with individual participant data. Dev Med Child Neurol 2019;61:49–56.

204. Jinnah HA, Alterman R, Klein C, et al. Deep brain stimulation for dystonia: a novel perspective on the value of genetic testing. J Neural Transm (Vienna) 2017;124:417–430.

205. Lumsden DE, Kaminska M, Gimeno H, et al. Proportion of life lived with dystonia inversely correlates with response to pallidal deep brain stimulation in both primary and secondary childhood dystonia. Dev Med Child Neurol 2013;55:567–574.

206. Markun LC, Starr PA, Air EL, Marks WJ, Jr., Volz MM, Ostrem JL. Shorter disease duration correlates with improved long-

term deep brain stimulation outcomes in young-onset DYT1 dystonia. Neurosurgery 2012;71:325–330.

207. Mikati MA, Yehya A, Darwish H, Karam P, Comair Y. Deep brain stimulation as a mode of treatment of early onset pantothenate kinase-associated neurodegeneration. Eur J Paediatr Neurol 2009; 13:61–64.

208. Timmermann L, Pauls KA, Wieland K, et al. Dystonia in neurodegeneration with brain iron accumulation: outcome of bilateral pallidal stimulation. Brain 2010;133(Pt 3):701–712.

209. De Vloo P, Lee DJ, Dallapiazza RF, et al. Deep brain stimulation for pantothenate kinase-associated neurodegeneration: a meta-analysis. Mov Disord 2019;34:264–273.

210. Vidailhet M, Yelnik J, Lagrange C, et al. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. Lancet Neurol 2009;8:709–717.

211. Chang FC, Westenberger A, Dale RC, et al. Phenotypic insights into ADCY5-associated disease. Mov Disord 2016;31:1033–1040.

212. Dy ME, Chang FC, Jesus SD, et al. Treatment of ADCY5-associated dystonia, chorea, and hyperkinetic disorders with deep brain stimulation: a multicenter case series. J Child Neurol 2016;31:1027–1035.

213. Meijer IA, Miravite J, Kopell BH, Lubarr N. Deep brain stimulation in an additional patient with ADCY5-related movement disorder. J Child Neurol 2017;32:438–439.

214. Aravamuthan BR, Waugh JL, Stone SS. Deep brain stimulation for monogenic dystonia. Curr Opin Pediatr 2017;29:691–696.

215. Bruggemann N, Kuhn A, Schneider SA, et al. Short- and long-term outcome of chronic pallidal neurostimulation in monogenic isolated dystonia. Neurology 2015;84:895–903.

216. Rughani AI, Lozano AM. Surgical treatment of myoclonus dystonia syndrome. Mov Disord 2013;28:282–287.

217. Magarinos-Ascone CM, Regidor I, Martinez-Castrillo JC, Gomez-Galan M, Figueiras-Mendez R. Pallidal stimulation relieves myoclonus-dystonia syndrome. J Neurol Neurosurg Psychiatry 2005;76:989–991.

218. Kuncel AM, Turner DA, Ozelius LJ, Greene PE, Grill WM, Stacy MA. Myoclonus and tremor response to thalamic deep brain stimulation parameters in a patient with inherited myoclonus-dystonia syndrome. Clin Neurol Neurosurg 2009;111:303–306.

219. Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet 2017;49:223–237.

220. Koy A, Cirak S, Gonzalez V, et al. Deep brain stimulation is effective in pediatric patients with GNAO1 associated severe hyperkinesia. J Neurol Sci 2018;391:31–39.

221. Honey CM, Malhotra AK, Tarailo-Graovac M, van Karnebeek CD, Horvath G, Sulistyanto A. GNAO1 mutation-induced pediatric dystonic storm rescue with pallidal deep brain stimulation. J Child Neurol 2018;33:413–416.

222. Yilmaz S, Turhan T, Ceylaner S, Gokben S, Tekgul H, Serdaroglu G. Excellent response to deep brain stimulation in a young girl with GNAO1-related progressive choreoathetosis. Childs Nerv Syst 2016;32:1567–1568.

223. Kulkarni N, Tang S, Bhardwaj R, Bernes S, Grebe TA. Progressive movement disorder in brothers carrying a GNAO1 mutation responsive to deep brain stimulation. J Child Neurol 2016;31: 211–214.

224. Deutschlander A, Asmus F, Gasser T, Steude U, Botzel K. Sporadic rapid-onset dystonia-parkinsonism syndrome: failure of bilateral pallidal stimulation. Mov Disord 2005;20:254–257.

225. Brücke C, Horn A, Huppke P, Kupsch A, Schneider GH, Kühn AA. Failure of pallidal deep brain stimulation in a case of rapid-onset dystonia parkinsonism (DYT 12). Mov Disord Clin Pract 2015;2:76–78.

226. Albanese A, Di Giovanni M, Amami P, Lalli S. Failure of pallidal deep brain stimulation in DYT12-ATP1A3 dystonia. Parkinsonism Relat Disord 2017;45:99–100.

227. Abejero JE, Jamora RD, Vesagas TS, et al. Long-term outcomes of pallidal deep brain stimulation in X-linked dystonia parkinsonism (XDP): Up to 84 months follow-up and review of literature. Parkinsonism Relat Disord 2018 Sep 21. pii: S1353-8020(18)30418-8. https://doi.org/10.1016/j.parkreldis.2018.09.022. [Epub ahead of print]

228. Martinez-Torres I, Limousin P, Tisch S, et al. Early and marked benefit with GPi DBS for Lubag syndrome presenting with rapidly progressive life-threatening dystonia. Mov Disord 2009;24:1710–1712.

229. Pauls KA, Timmermann L. Deep brain stimulation in pantothenate kinase associated neurodegeneration: challenges for the future. Eur J Neurol 2012;19:533–534.

230. Castelnau P, Cif L, Valente EM, et al. Pallidal stimulation improves pantothenate kinase-associated neurodegeneration. Ann Neurol 2005;57:738–741.

231. Krause M, Fogel W, Tronnier V, et al. Long-term benefit to pallidal deep brain stimulation in a case of dystonia secondary to pantothenate kinase-associated neurodegeneration. Mov Disord 2006;21: 2255–2257.

232. Hogarth P, Kurian MA, Gregory A, et al. Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). Mol Genet Metab 2017;120:278–287.

233. Liu Z, Liu Y, Yang Y, et al. Subthalamic nuclei stimulation in patients with pantothenate kinase-associated neurodegeneration (PKAN). Neuromodulation 2017;20:484–491.

234. Elia AE, Bagella CF, Ferre F, Zorzi G, Calandrella D, Romito LM. Deep brain stimulation for dystonia due to cerebral palsy: a review. Eur J Paediatr Neurol 2018;22:308–315.

235. Koy A, Timmermann L. Deep brain stimulation in cerebral palsy: challenges and opportunities. Eur J Paediatr Neurol 2017;21: 118–121.

236. Shaikh AG, Mewes K, DeLong MR, et al. Temporal profile of improvement of tardive dystonia after globus pallidus deep brain stimulation. Parkinsonism Relat Disord 2015;21:116–119.

237. Trottenberg T, Volkmann J, Deuschl G, et al. Treatment of severe tardive dystonia with pallidal deep brain stimulation. Neurology 2005;64:344–346.

238. Gruber D, Trottenberg T, Kivi A, et al. Long-term effects of pallidal deep brain stimulation in tardive dystonia. Neurology 2009; 73:53–58.

239. Sako W, Goto S, Shimazu H, et al. Bilateral deep brain stimulation of the globus pallidus internus in tardive dystonia. Mov Disord 2008;23:1929–1931.

240. Schrock LE, Mink JW, Woods DW, et al. Tourette syndrome deep brain stimulation: a review and updated recommendations. Mov Disord 2015;30:448–471.

241. Dressler D, Berweck S, Chatzikalfas A, et al. Intrathecal Baclofen therapy in Germany: Proceedings of the IAB-Interdisciplinary Working Group for Movement Disorders Consensus Meeting. J Neural Transm (Vienna) 2015;122:1573–1579.

242. Hasnat MJ, Rice JE. Intrathecal baclofen for treating spasticity in children with cerebral palsy. Cochrane Database Syst Rev 2015; (11):CD004552.

243. Dwarakanath S, Zafar A, Yadav R, et al. Does lesioning surgery have a role in the management of multietiological tremor in the era of deep brain stimulation? Clin Neurol Neurosurg 2014;125: 131–136.

244. Meng Y, Solomon B, Boutet A, et al. Magnetic resonance-guided focused ultrasound thalamotomy for treatment of essential tremor: a 2-year outcome study. Mov Disord 2018;33:1647–1650.

245. Rohani M, Fasano A. Focused ultrasound for essential tremor: review of the evidence and discussion of current hurdles. Tremor Other Hyperkinet Mov (N Y) 2017;7:462.

246. Udupa K, Chen R. Central motor conduction time. Handb Clin Neurol 2013;116:375–386.

247. Kirton A. Advancing non-invasive neuromodulation clinical trials in children: lessons from perinatal stroke. Eur J Paediatr Neurol 2017;21:75–103.

248. Kirton A, Andersen J, Herrero M, et al. Brain stimulation and constraint for perinatal stroke hemiparesis: the PLASTIC CHAMPS Trial. Neurology 2016;86:1659–1667.

249. Sanger TD, Chen D, Delgado MR, et al. Definition and classification of negative motor signs in childhood. Pediatrics 2006;118:2159–2167.

250. Moreau NG, Bodkin AW, Bjornson K, Hobbs A, Soileau M, Lahasky K. Effectiveness of rehabilitation interventions to improve gait speed in children with cerebral palsy: systematic review and meta-analysis. Phys Ther 2016;96:1938–1954.

251. Sakzewski L, Ziviani J, Boyd RN. Efficacy of upper limb therapies for unilateral cerebral palsy: a meta-analysis. Pediatrics 2014;133: e175–e204.

252. Wells H, Marquez J, Wakely L. Garment therapy does not improve function in children with cerebral palsy: a systematic review. Phys Occup Ther Pediatr 2018;38:395–416.

253. Loeters MJ, Maathuis CG, Hadders-Algra M. Risk factors for emergence and progression of scoliosis in children with severe cerebral palsy: a systematic review. Dev Med Child Neurol 2010;52:605–611.

254. Parrott J, Boyd RN, Dobson F, et al. Hip displacement in spastic cerebral palsy: repeatability of radiologic measurement. J Pediatr Orthop 2002;22:660–667.

255. Hirschtritt ME, Lee PC, Pauls DL, et al. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry 2015;72:325–333.

256. Peall KJ, Lorentzos MS, Heyman I, et al. A review of psychiatric co-morbidity described in genetic and immune mediated movement disorders. Neurosci Biobehav Rev 2017;80:23–35.

257. Harris KM, Mahone EM, Singer HS. Nonautistic motor stereotypies: clinical features and longitudinal follow-up. Pediatr Neurol 2008;38:267–272.

258. Gadow KD, Sverd J, Nolan EE, Sprafkin J, Schneider J. Immediate-release methylphenidate for ADHD in children with comorbid chronic multiple tic disorder. J Am Acad Child Adolesc Psychiatry 2007;46:840–848.

259. Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology 2002;58: 527–536.

260. Allen AJ, Kurlan RM, Gilbert DL, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. Neurology 2005;65:1941–1949.

261. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev 2018;6: Cd007990.