Emerging therapies for childhood-onset movement disorders

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Purpose of review
We highlight novel and emerging therapies in the treatment of childhood-onset movement disorders. We structured this review by therapeutic entity (small molecule drugs, RNA-targeted therapeutics, gene replacement therapy, and neuromodulation), recognizing that there are two main approaches to treatment: symptomatic (based on phenomenology) and molecular mechanism-based therapy or 'precision medicine' (which is disease-modifying).

Recent findings
We highlight reports of new small molecule drugs for Tourette syndrome, Friedreich's ataxia and Rett syndrome. We also discuss developments in gene therapy for aromatic l-amino acid decarboxylase deficiency and hereditary spastic paraplegia, as well as current work exploring optimization of deep brain stimulation and lesioning with focused ultrasound.

Summary
Childhood-onset movement disorders have traditionally been treated symptomatically based on phenomenology, but focus has recently shifted toward targeted molecular mechanism-based therapeutics. The development of precision therapies is driven by increasing capabilities for genetic testing and a better delineation of the underlying disease mechanisms. We highlight novel and exciting approaches to the treatment of genetic childhood-onset movement disorders while also discussing general challenges in therapy development for rare diseases. We provide a framework for molecular mechanism-based treatment approaches, a summary of specific treatments for various movement disorders, and a clinical trial readiness framework.

Keywords
deep brain stimulation, gene therapy, movement disorders, neurogenetics, precision medicine

INTRODUCTION

Movement disorders are a group of neurological disorders in which patients face challenges with the control and execution of movements. Traditionally, movement disorders have been classified by *phenomenology*: excess activation of central motor pathways (*hyperkinetic*: dystonia, chorea, athetosis, myoclonus, stereotypies, tics, tremor); decreased voluntary motor function (*hypokinetic*: hypo/bradykinesia, rigidity); impaired coordination (e.g. ataxia); and changes in muscle tone (i.e. spasticity). As phenomenology does not reflect causality, movement disorders need to be further differentiated by cause (e.g. genetic/primary or acquired/secondary).

Phenomenology, in addition to serving as the basis for classification, has traditionally guided treatment approaches. Symptomatic treatments such as medications (e.g. levodopa/dopamine receptor agonists, anticholinergics, and benzodiazepines) or surgical procedures (e.g. deep brain stimulation or selective dorsal rhizotomy) target the phenomenology rather than the underlying molecular cause. Benefits of this approach include the use of common strategies to treat symptoms across different causes. Limitations include challenges of treating patients

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KEY POINTS

- Therapeutic modalities for childhood-onset movement disorders target disease mechanisms at DNA, RNA, protein, cellular and circuit levels.
- There is not only a growing list of specific symptomatic treatments but also molecular mechanism-based disease modifying therapies.
- There are not only unique challenges but also opportunities for creating therapies for childhood-onset movement disorders.
- Broad access to genetic testing and longitudinal natural history studies are key to establishing clinical trial readiness.

with mixed movement disorders, adjusting to changes in phenomenology over time, medication side effects, interactions and polypharmacy, as well as the inability to address disease-associated comorbidities (e.g. developmental delay or epilepsy).

With increasing capacity for genetic diagnostics, two important concepts have emerged: genetic heterogeneity – one phenotype caused by variants in several genes; and phenotypic pleiotropy – variants of the same gene causing several movement disorders. These concepts, combined with an increased understanding of disease mechanisms, and the limitations of available symptomatic therapies, have led to a push toward molecular-mechanism-based treatments ('precision medicine'). We define these as disease-modifying therapies that are rationally targeted against specific molecular structures implicated in disease pathogenesis.

In this review, we summarize recent developments in both symptomatic and molecular mechanism-based treatments for childhood-onset movement disorders, with a focus on emerging themes. We have categorized these novel approaches by mechanism (Fig. 1) and target level (Fig. 2).

SMALL MOLECULE DRUGS

Small molecule drugs remain a cornerstone of therapeutics because of their ease of delivery and relatively lower manufacturing costs. Many small molecule therapies are symptomatic therapies that have been used for decades. Some small molecule drugs have demonstrated higher efficacy in specific diseases (Table 1 and Fig. 2), allowing a more targeted approach.

Ecicopam for Tourette syndrome

Tourette syndrome is a neuropsychiatric disorder characterized by persistent vocal and motor tics that can be disruptive to day-to-day life. The gold standard treatment for Tourette syndrome is comprehensive behavioral intervention for tics [1]; however, many children require adjunctive pharmacotherapy. Traditional dopamine antagonists are often limited by side effects. Ecicopam is a more selective dopamine 1 receptor antagonist, which was proven to be effective in a recent double-blind, randomized, placebo-controlled trial. Importantly, there were fewer side effects, including less weight gain and no drug-induced movement disorders [2▪▪].

High-flow oxygen for *ATP1A3*-related alternating hemiplegia of childhood

Alternating hemiplegia of childhood is a disorder on the *ATP1A3* spectrum [3] causing paroxysmal attacks of unilateral or bilateral weakness or dystonia [4]. Flunarizine, the most used medication, has variable effectiveness. Recent case reports highlighted that early treatment with high-flow oxygen may help shorten attacks [5,6]. High-flow oxygen had no effect on event frequency but improved quality of life, allowing for reduced benzodiazepine use [6]. This requires further research, ideally in blinded placebo-controlled trials.

Cannabinoids

Since the introduction of cannabinoids for epilepsy and chronic pain, there has been increasing interest in using cannabinoids for symptomatic treatment of dystonia. A trial in 2018 demonstrated improvement in spasticity, dystonia, and quality of life in patients treated with two formulations of cannabis. This was limited by a small sample size and lack of a control group [7]. Further studies are needed to define the role of cannabinoids in childhood-onset movement disorders.

Stimulants for paroxysmal movement disorders

Paroxysmal movement disorders are a clinically and molecularly heterogeneous group. For some, such as *PRRT2*-associated paroxysmal kinesigenic dyskinesia, specific treatments exist [8]. There is evolving evidence to support the use of stimulants: Lisdexamfetamine [9] and dextroamphetamine [10] have been shown to benefit nonkinesigenic paroxysmal dyskinesia in cases of *KCNMA1*-related disorder, and methylphenidate has been observed to improve chorea in cases of *NKX2.1*-related disorder [11,12].

Caffeine for *ADCY5*-related disorder

Heterozygous variants in *ADCY5*, encoding adenylyl cyclase 5, lead to a hyperkinetic movement disorder

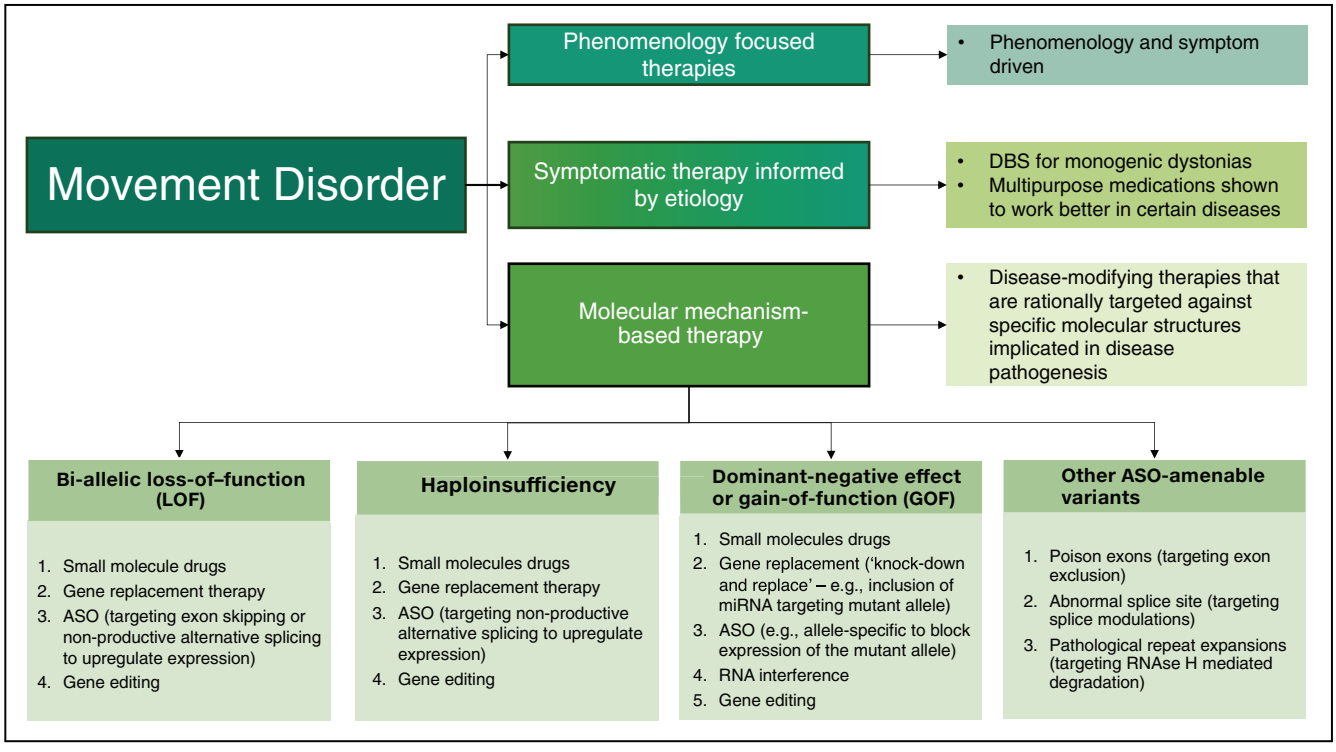

FIGURE 1. Overview of existing and emerging therapies fall for childhood-onset movement disorders. Therapeutic approaches fall into three categories: traditional phenomenology-based symptomatic treatment approaches which includes small molecule drugs, nonpharmacological treatments (e.g. physical therapy, equipment and adaptive devices), and invasive or surgical approaches (i.e. botulinum toxin injections, selective dorsal rhizotomy, or deep brain stimulation). A subset of phenomenology-based approaches has established efficacy in specific causes, these are further highlighted in Table 1 and include small molecule drugs (e.g. carbamazepine for paroxysmal kinesigenic dyskinesia), dietary treatments (e.g. ketogenic diet for paroxysmal exercise-induced dyskinesia), and deep brain stimulation (e.g. for *TOR1A*-associated dystonia). An emerging and growing category of newer treatments is based on the molecule mechanism, usually for genetic movement disorders. We defined these as disease-modifying therapies that are rationally targeted against specific molecular structures implicated in disease pathogenesis. A crucial first step is the recognition of the main cell autonomous molecular mechanism upstream of cellular, metabolic or circuitry changes. Broad categories include bi-allelic loss-of-function variants, heterozygous variants leading to haploinsufficiency, and heterozygous variants leading to a dominant-negative effects or toxic gain of function. Different therapeutic entities can be rationally chosen and matched to these key mechanisms, supporting testing and development as highlighted in Fig. 3. Additionally, specific variants, often in individual cases or small number of individuals, might be amenable to antisense oligonucleotide (ASO), the classic example would be variants that introduce a cryptic splice site that can be blocked to restore a normal splicing pattern.

with early-onset chorea, dystonia, myoclonus, nocturnal dyskinesia, and characteristic facial dyskinesia [13]. Most variants causing *ADCY5*-related disorder are believed to be gain-of-function mutations resulting in increased cAMP levels in striatal neurons [14]. Adenosine 2A antagonists, including caffeine, have thus been explored as therapeutics. A retrospective survey of 30 patients treated with caffeine [15] reported significant improvement in dyskinesia, with improvement also noted in hypotonia, dysarthria, pain, attention, concentration, sleep quality, and mood in some. Given the relatively good safety profile, a trial of caffeine, in addition to other treatment options, should be considered.

Chelation for pantothenate kinase-associated neurodegeneration

Pantothenate kinase-associated neurodegeneration (PKAN) is a form of neurodegeneration with brain iron accumulation that presents with progressive dystonia and parkinsonism [16]. The iron chelator, deferiprone, was tested in a randomized, double-blind, placebo-controlled trial [17]. Deferiprone reduced iron storage in the brain and improved dystonia in patients with late-onset PKAN (after age 6 years), but not early-onset PKAN [17]. This study was limited by small sample size and study duration. It is unclear if further studies will attempt to confirm the use of chelation therapy, as more

FIGURE 2. Therapeutic levels targeted by existing and emerging therapies for childhood-onset movement disorders. Childhood-onset movement disorders can be understood at different levels, ranging from variants in DNA to complex phenomenology. Each ascending level is the results of the sum or composite of the preceding level. By understanding and appreciating disease mechanisms at different level, therapeutic targets and entities can be developed and tailored. Examples of existing and emerging therapies are matched to the appropriate level. AADC, aromatic l-amino acid decarboxylase; ADCY5, adenylyl cyclase 5; FRDA, Friedreich's Ataxia; NMDA-RE, *N*-methyl-D-aspartate receptor encephalitis; OT, occupational therapy; PED, paroxysmal exercise induced dyskinesia; PT, physical therapy; SPG50, spastic paraplegia 50; VMAT2, vesicular monoamine transporter 2.

Table 1. Existing therapeutics for childhood-onset movement disorders that are informed by the underlying cause

Disorder	Gene	Leading phenomenology	Treatment	Level of evidence[a]
ADCY5-related disorder (CHOR/DYT-*ADCY5*)	*ADCY5*	Chorea, dystonia	Caffeine	4 [15]
			Theophylline	4 [38]
Alternating Hemiplegia of Childhood	*ATP1A3*	Hemiparesis, dystonia	Flunarizine	4 [39,40]
			High-flow oxygen	4 [6]
Aromatic l-amino acid decarboxylase (AADC) deficiency	*DDC*	Dystonia	Eladocagene exuparvovec	3b [59]
Ataxia telangiectasia	*ATM*	Ataxia	Nicotinamide	3c [41]
Ataxia with vitamin E deficiency	*TTPA*	Ataxia	High-dose vitamin E	4 [42]
Cerebrotendinous xanthomatosis	*CYP27A1*	Ataxia, spasticity	Chenodeoxycholic acid	4 [43]
Dopa-responsive dystonia (DYT/PARK-*GCH1*, Segawa disease)	*GCH1*	Dystonia	Levodopa	4 [44]
Episodic ataxia 1	*KCNA1*	Ataxia	Acetazolamide	3b [45]
			Carbamazepine	3b [45]
Episodic ataxia 2	*CACNA1A*	Ataxia	Acetazolamide	3b [46]
			4-aminopyridine	4 [47]
Friedreich's ataxia	*FXN*	Ataxia	Omaveloxolone	1 [20]
GNAO1-related disorder (DYT/CHOR-*GNAO1*)	*GNAO1*	Chorea, dystonia	Zinc	5 [26▪▪]
Hereditary spastic paraplegia type 50 (SPG50, HSP-*AP4M1*)	*AP4M1*	Spasticity	AAV9/AP4M1	5 [63]
Hypermanganesemia	*SLC30A10SLC39A14*	Dystonia	Intravenous sodium calcium edetate	4 [48]
Myoclonus-dystonia (DYT-*SGCE*)	*SGCE*	Myoclonus, dystonia	Zonisamide	1 [49]
NKX2.1-related disorder (CHOR-*NKX2.1*, brain-lung-thyroid disease)	*NKX2.1*	Chorea	Methylphenidate	4 [11]
Pantothenate kinase-associated neurodegeneration (NBIA/DYT-*PANK2*)	*PANK2*	Dystonia	Deferiprone	1 [17]
Paroxysmal exercise induced dyskinesia/GLUT1 deficiency	*SLC2A1*	Choreoathetosis, dystonia	Ketogenic diet	3c [50]
Paroxysmal kinesigenic dyskinesia (PxMd-*PRRT2*)	*PRRT2*	Paroxysmal dyskinesia (chorea, dystonia)	Carbamazepine	3b [8]
Paroxysmal nonkinesigenic dyskinesia	*PNKD*	Paroxysmal dyskinesia (dystonia, chorea)	Oxcarbazepine	4 [51]
			Clonazepam	4 [52]
	KCNMA1	Paroxysmal dyskinesia (chorea, dystonia), ataxia, cataplexy	Lisdexamfetamine	4 [9]
Pyruvate dehydrogenase deficiency	*DLAT, PDHA1, PDHB, PDHX, PDP1, PDK3*	Ataxia, dystonia, paroxysmal dyskinesia	Ketogenic diet	4 [53]
Rett syndrome	*MECP2*	Stereotypies, dystonia	Trofinetide	1 [24▪▪]
Biotin-thiamine-responsive basal ganglia disease	*SLC19A3*	Dystonia	Thiamin +/- biotin	4 [54]
Tourette syndrome	–	Tics	Ecopipam	1 [2▪▪]
Wilson's disease	*ATP7B*	Dystonia	D-penicillamine	3b [55]

[a]Levels of evidence: 1 – evidence obtained from a systematic review of all relevant randomized control trials; 2a – evidence obtained from at least one properly designed randomized control trial; 3a – evidence obtained from well designed pseudo-randomized control trials (alternative allocation); 3b – evidence obtained from comparative studies (including systematic review of such studies) with concurrent controls, case–control studies, interrupted time series with a control group; 3c – evidence obtained from comparative studies with historical control, two or more single arm studies, interrupted time series without a parallel control group; 4 – evidence obtained from case series; 5 – evidence obtained from expert opinion without clinical appraisal, or based on physiology, based on bench research or historically based clinical principles.

targeted gene-based therapies are under development [18].

Omaveloxolone for Friedreich's ataxia

Friedreich's ataxia (FRDA) is an autosomal-recessive triplet-repeat disorder causing a syndrome of progressive ataxia, cerebellar dysfunction, sensory neuropathy, lower limb spasticity, and hypertrophic cardiomyopathy. Oxidative stress is a prevailing disease mechanism in FRDA. Omaveloxolone, a nuclear factor erythroid 2-related factor 2 and nuclear factor kappa B inhibitor, is implicated in cellular response to oxidative injury [19]. Based on a

positive double-blind, randomized, placebo-controlled study, the Food and Drug Administration (FDA) approved omaveloxolone for patients older than 16 years, with the caveat that younger patients may have better response [20–22]. The impact on disease progression long-term remains to be established [21].

Trofenitide for Rett syndrome

Heterozygous loss-of-function variants in *MECP2* cause Rett syndrome in female individuals, a progressive neurodevelopmental disorder characterized by regression of language and motor skills, epilepsy, and prominent movement disorders, including dystonia and stereotypies. Trofinetide is a synthetic analog of glycine-proline-glutamate, the N-terminal tripeptide of the insulin-like growth factor 1, with multiple putative mechanisms of action [23]. A recent phase 3 study demonstrated improvement in Rett syndrome-associated behaviors and global impression, including motor skills [24▪▪], leading to FDA-approval for ages 2 and older [23]. The impact of trofinetide on movement disorders in Rett syndrome remains to be established.

Future promise in small molecule therapies

Despite advances in our ability to delineate the genetic causes of rare neurological diseases, it is estimated that specific therapies exist for less than 5%. Informed by disease-relevant cellular phenotypes, automated and unbiased high-throughput small molecule screens have the potential to uncover new therapeutic targets. This approach is starting to be applied to rare genetic movement disorders, with promising preclinical results. Examples include the recent discovery of a novel small molecule modulator of protein trafficking for adaptor-protein complex 4-related hereditary spastic paraplegia [25▪▪] and zinc as a novel treatment for *GNAO1*-related disorder [26▪▪].

RNA-TARGETED THERAPIES

Antisense oligonucleotides (ASO) are an increasingly common targeted therapy in neurology [27]. ASO therapy involves single-stranded antisense oligonucleotides, which are delivered to tissues of interest and subsequently exert their effect on gene expression. Their effects can range from degradation of the target RNA transcript, blocking translation of a specific region, or performing splicing modification [28] (Figs. 1 and 2). ASOs targeting the CNS are delivered intrathecally to circumvent the blood–brain barrier. In addition to ASOs, other techniques that act on RNA include small molecule splice modifiers or RNA interference [27].

Antisense oligonucleotides in Huntington's disease

Huntington's disease is an autosomal-dominant trinucleotide repeat disorder thought to result from toxicity of mutant huntingtin protein. ASO therapy attempts to reverse this by lowering levels of mutant huntingtin. Clinical trials have been controversial. Tominersen, which targets wild-type and mutant huntingtin, showed efficacy in transgenic animal models and target engagement in individuals with Huntington's disease, leading to a dose-dependent reduction in cerebrospinal fluid (CSF) levels of huntingtin [29]. A recent phase 3 study, however, was stopped after no benefit was observed and a subset of treated patients showed decline compared with placebo [30▪▪]. Post hoc analyses suggested that younger participants may benefit from tominersen. This hypothesis is being tested in a phase 2 trial (NCT05686551). Other ASO approaches to Huntington's disease include allele-selective ASO which lack potential detrimental effects from impairing wild-type huntingtin protein but are limited by the inability to target the entire Huntington's disease population and potential off-target effects. New therapies including RNAi are currently being investigated [31].

Preclinical antisense oligonucleotide therapy in ataxia telangiectasia

Ataxia telangiectasia is an autosomal-recessive progressive ataxia caused by homozygous loss-of-function variants in *ATM*. This causes decreased ability to repair DNA double-strand breaks, leading to progressive cerebellar ataxia, immunodeficiency, and increased risk for malignancies. A recent article highlighted personalized targets for splice switching ASOs in ataxia telangiectasia, depending on the specific variants [32]. Although this is entirely preclinical, the framework shows promise for developing ASOs for a subset of ataxia telangiectasia patients.

GENE REPLACEMENT

Gene replacement therapy for childhood-onset movement disorders is an area of extensive research [33,34] (Table 1 and Figs. 1 and 2). Current approaches were made possible by the success of AAV9-based gene replacement for spinal muscular atrophy [35]. For CNS disorders, the most common

vectors for transgene delivery remain the adeno-associated viruses (AAVs) given their tropism and relative safety [36]. Current vectors have limitations in their transgene capacity, biodistribution, the immune-response to the capsid protein, and potential transgene overexpression related toxicity [37].

Intraparenchymal gene replacement in aromatic l-amino acid decarboxylase deficiency

Aromatic l-amino acid decarboxylase (AADC) is an enzyme that catalyzes the transformation of levodopa to dopamine, as well as precursors of other amino acid neurotransmitters into their final product (serotonin, norepinephrine, epinephrine). Patients with AADC deficiency suffer from early-onset severe dystonia, oculogyric crises, axial hypotonia, and bulbar dysfunction and often die early in life because of medical complications [56]. Building on initial work for Parkinson's disease, an intraparenchymal AAV2-mediated gene therapy for AADC deficiency was developed. This gene therapy was first introduced in Taiwan (where there is a higher prevalence because of a founder allele) [57]. Stereotactic delivery to the putamen reduced the frequency of dyskinesia and oculogyric crises, improving functional outcomes [58–60]. This putaminal gene therapy, eladocagene exuparvovec, was approved by the EU in 2022 [61] and a recently proposed model predicts that it extends survival by 25 years and lowers healthcare costs [62]. A second AAV2 gene therapy vector for AADC deficiency targeted to the substantia nigra and ventral tegmental areas is in clinical trials and may be even more effective because of more specific targeting of dopaminergic pathways [58].

Intrathecal gene replacement for spastic paraplegia type 50

Hereditary spastic paraplegia type 50 (or SPG50) is a rare form of complex childhood-onset hereditary spastic paraplegia characterized by progressive lower limb spasticity, developmental delay and intellectual disability, epilepsy, secondary microcephaly, and brain malformations. An interdisciplinary investigator team recently developed an intrathecal AAV9-based gene therapy from concept to first-in-human use in less than 3 years [63]. This highlights the potential for similar approaches to other forms of hereditary spastic paraplegia and pediatric movement disorders due to a loss-of-function mechanism. The gene therapy for SPG50 is currently in phase 1/2 study (NCT05518188).

GENE EDITING

Gene editing has the potential to become a transformative platform technology that can target many monogenic diseases (Figs. 1 and 2). Recent advances in hematological diseases where gene editing is employed *ex vivo* highlight this potential [64]. For central nervous system diseases, delivery and efficacy remain significant barriers.

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) involves stereotactic implantation of depth electrodes to specific CNS areas. Electrodes are connected to a battery that delivers pulses of current at a specific amplitude, frequency, and duration to modulate neuronal circuitry (Fig. 2) [65,66].

Deep brain stimulation for genetic movement disorders in children

With increasing use of DBS (most commonly targeting the globus pallidus pars internus – GPi), there have been multiple observations that DBS is more effective in children with monogenic forms of dystonia or dyskinesia (particularly *TOR1A* [67], *GNAO1* [68] and *KMT2B* [69]). In addition, there is emerging evidence for a positive response to GPi DBS in an evolving number of other rare childhood-onset movement disorders (*ACTB* [70], *ADCY5* [71], *ANO3* [72], *EIF2AK2* [73], *PANK2* [74], *SGCE* [75], *TAF1* [76], *THAP1* [77], *UBA5* [78]). Independent of cause, an important application of DBS is in the setting of status dystonicus and refractory status dystonicus [79▪▪,80,81].

Deep brain stimulation in Tourette syndrome and self-injurious behaviors

The use of DBS for severe and pharmaco-resistant Tourette syndrome in childhood is controversial, given its potential for not only improvement but also the invasive nature, risk of complications, and the natural history of Tourette syndrome to improve with maturity [82]. Target areas include the thalamic centromedian parafascicular complex and the GPi [83]. Patient selection is key, with prior work proposing failure of behavioral and pharmacologic therapies, high tic severity and negative impact on quality of life as criteria [84]. Also, at the intersection of movement disorders and neurodevelopmental psychiatry are self-injurious behaviors for which DBS is a promising intervention, although more studies are needed [85].

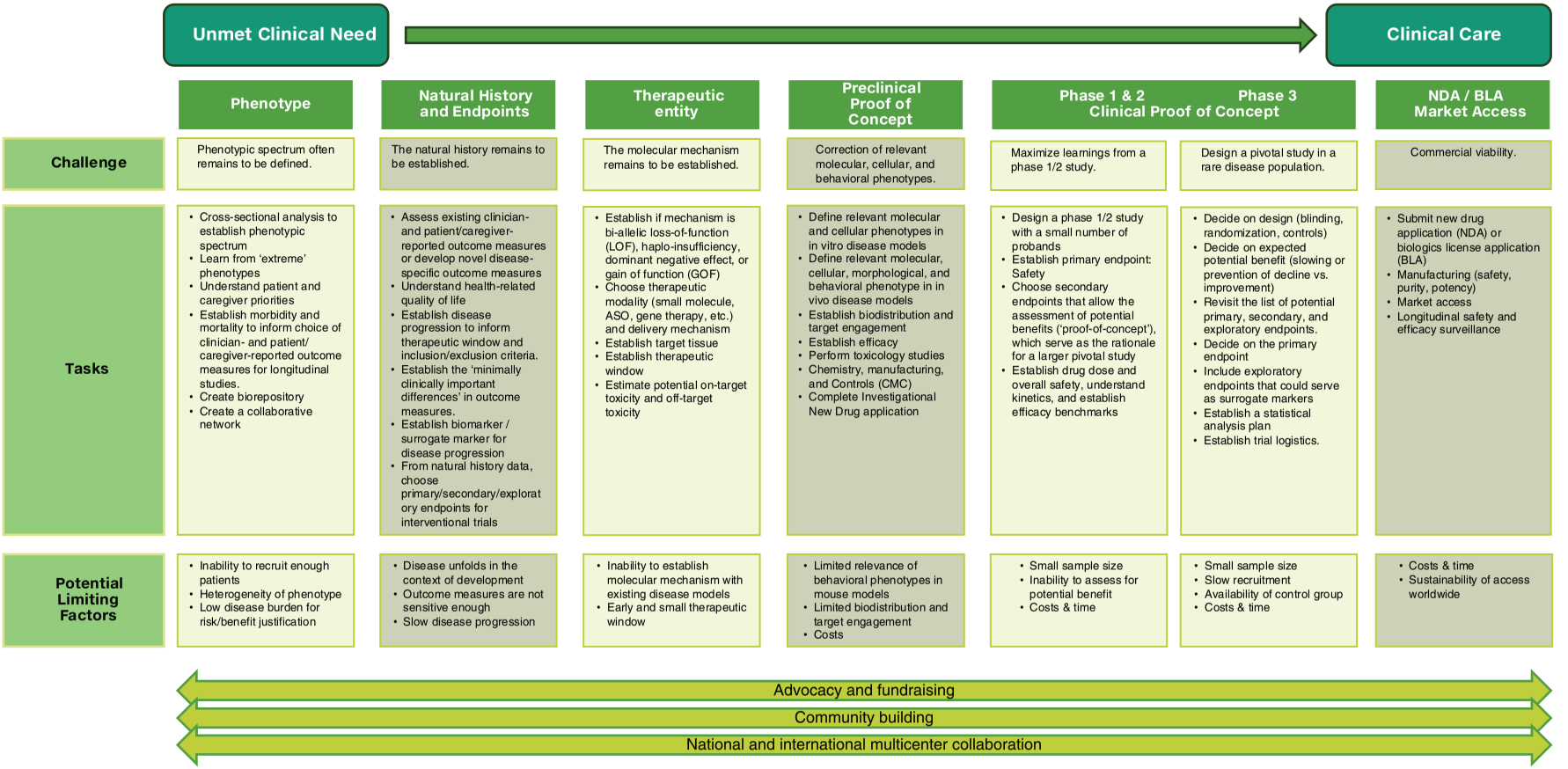

FIGURE 3. A framework for the development of novel therapeutics for childhood-onset movement disorders and other rare diseases. In the era of advancing genetic disorder identification, conducting structured multicenter studies is imperative for comprehensively documenting the natural history of rare diseases and establishing the necessary infrastructure for evaluating emerging therapies. The framework presented here highlights key steps between the recognition of an unmet clinical need and the implementation of a new therapy in clinical care. Emphasis is placed on the early recognition and implementation of key tasks at every step of the development pipeline. Potential challenges and limiting factors are also highlighted. The initial pivotal step involves access to genomic platforms capable of pinpointing causative variant(s) and highlighting potential molecular mechanism-based therapeutic avenues. Recognizing these conditions early is paramount, particularly given that the therapeutic window for progressive movement disorders may be narrower than currently estimated. Although cross-sectional phenotyping studies contribute to understanding the spectrum of disease manifestations, subsequent prospective longitudinal natural history studies become essential. These studies play a crucial role in defining disease progression, assessing morbidity and mortality (thereby informing risk–benefit discussions for experimental therapeutics), and evaluating potential biomarkers and endpoints for interventional trials. In the preclinical development phase of novel mechanism-based therapies, the establishment of key molecular or cellular disease phenotypes in disease models facilitates in-vitro and in-vivo proof-of-concept experiments. Upon completing IND-enabling studies, the design of phase 1/2 trials becomes a notable challenge, requiring not only safety testing but also the maximization of insights derived from secondary endpoints assessing efficacy. Subsequent studies encounter difficulties associated with small patient populations and the need to demonstrate meaningful benefits, such as improvement or, more realistically, a slowing of progression within a relatively short timeframe. The high costs related to manufacturing and pivotal studies pose a significant hurdle, making some programs commercially nonviable. This underscores the critical importance of developing platform technologies to mitigate costs, fostering a supportive regulatory environment, and promoting innovative, investigator-driven, and grant-funded clinical studies that effectively de-risk novel therapeutic approaches for the rare disease community.

FOCUSED ULTRASOUND FOR LESIONING

MRI-guided focused ultrasound for thalamotomy is now an established treatment for essential tremor and Parkinson's disease in adults. There is growing interest in applying this approach to refractory dystonia in children, with a clinical trial looking to compare focused ultrasound-induced pallidotomy versus GPi-DBS in treatment-refractory dystonia in dyskinetic cerebral palsy (NCT06036199).

FUTURE CHALLENGES IN IMPROVING THE TREATMENT OF PEDIATRIC MOVEMENT DISORDERS

With increasing identification of genetic disorders, structured multicenter studies are crucial to document the natural history of rare diseases and to build infrastructure to test emerging therapies (Fig. 3). Access to genomic platforms that delineate the causative variant(s) and flag potential molecular mechanism-based therapies is the initial step. Early recognition is key as the therapeutic window for progressive movement disorders is likely smaller than currently anticipated. Cross-sectional phenotyping studies can establish the range of disease manifestations, but subsequent prospective, longitudinal natural history studies are needed to define disease progression, morbidity and mortality (which inform risk/benefit discussions for experimental therapeutics), and for testing potential biomarkers and endpoints for interventional trials. In the preclinical development of novel mechanism-based therapies, establishing key molecular or cellular disease phenotypes in disease models allows for in-vitro and in-vivo proof-of-concept experiments. Following IND-enabling studies, a particular challenge exists in designing phase 1/2 studies to not only test safety but also maximize learnings from secondary endpoints assessing efficacy. Subsequent studies face the challenge of small patient populations and needing to demonstrate meaningful benefit (improvement or, more likely, slowing of progression) in a relatively short time. Additional challenges exist in the high cost associated with manufacturing and pivotal studies, rendering some programs commercially nonviable. This underscores the importance of developing platform technologies to mitigate costs, a supportive regulatory environment, and innovative, investigator-driven, and grant-funded clinical studies that de-risk novel therapeutic approaches to the benefit of the rare disease community.

To address some of these issues, the concept of '*Clinical Trial Readiness*' has arisen. We define clinical trial readiness as a state of having validated clinical research tools and disease natural history necessary for the design of efficient clinical trials. We provide a checklist for clinical trial readiness in Fig. 3.

CONCLUSION

The field of childhood-onset movement disorders remains one of the most exciting and complex within neurology. Several therapeutic modalities treat underlying genetic/protein and cell-based pathophysiology to network dysfunction and symptoms. Children with movement disorders that are not adequately managed on their current treatment regimen should be referred to pediatric movement disorder specialists and multidisciplinary tertiary care clinics where treatment can be optimized and enrollment in research studies is facilitated.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Pringsheim T, Okun MS, Muller-Vahl K, *et al.* Practice guideline recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology 2019; 92:896–906.
2. ■■ Gilbert DL, Dubow JS, Cunniff TM, *et al.* Ecopipam for Tourette syndrome: a randomized trial. Pediatrics 2023; 151:e2022059574.
This multicenter, randomized, double-blind, placebo-controlled, phase 2b trial demonstrated reduced total tic scores from baseline to 12 weeks. Importantly there were no observable evidence of common antipsychotic-associated side effects.
3. Vezyroglou A, Akilapa R, Barwick K, *et al.* The phenotypic continuum of ATP1A3-related disorders. Neurology 2022; 99:e1511–e1526.
4. Mikati MA, Panagiotakaki E, Arzimanoglou A. Revision of the diagnostic criteria of alternating hemiplegia of childhood. Eur J Paediatr Neurol 2021; 32:A4–A5.
5. Welniarz Q, Gras D, Roubertie A, *et al.* Oxygen therapy: an acute treatment for paroxysmal dystonia in alternating hemiplegia of childhood? Mov Disord 2023; 38:906–907.

6. Papadopoulou MT, Welniarz Q, Roubertie A, *et al.* Effect of oxygen administration on paroxysmal motor events in alternating hemiplegia of childhood. Mov Disord 2023; 38:1759–1761.
7. Libzon S, Schleider LB, Saban N, *et al.* Medical cannabis for pediatric moderate to severe complex motor disorders. J Child Neurol 2018; 33:565–571.
8. Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. Brain 2015; 138(Pt 12):3476–3495.
9. Keros S, Heim J, Hakami W, *et al.* Lisdexamfetamine therapy in paroxysmal nonkinesigenic dyskinesia associated with the KCNMA1-N999S variant. Mov Disord Clin Pract 2022; 9:229–235.
10. Zhang G, Gibson RA, McDonald M, *et al.* A gain-of-function mutation in KCNMA1 causes dystonia spells controlled with stimulant therapy. Mov Disord 2020; 35:1868–1873.
11. Tubing J, Bohnenpoll J, Spiegler J, *et al.* Methylphenidate can improve chorea in NKX2.1 and ADCY5 mutation-positive patients-a report of two children. Mov Disord Clin Pract 2018; 5:343–345.
12. Gauquelin L, Tran LT, Chouinard S, Bernard G. The movement disorder of brain-lung-thyroid syndrome can be responsive to methylphenidate. Tremor Other Hyperkinet Mov (N Y) 2017; 7:508.
13. Menon PJ, Nilles C, Silveira-Moriyama L, *et al.* Scoping review on ADCY5-related movement disorders. Mov Disord Clin Pract 2023; 10:1048–1059.
14. Chen YZ, Friedman JR, Chen DH, *et al.* Gain-of-function ADCY5 mutations in familial dyskinesia with facial myokymia. Ann Neurol 2014; 75:542–549.
15. Meneret A, Mohammad SS, Cif L, *et al.* Efficacy of caffeine in ADCY5-related dyskinesia: a retrospective study. Mov Disord 2022; 37:1294–1298.
16. Sriram N, Holla VV, Kumari R, *et al.* Clinical, imaging and genetic profile of twenty-four patients with pantothenate kinase-associated neurodegeneration (PKAN)- a single centre study from India. Parkinsonism Relat Disord 2023; 111:105409.
17. Klopstock T, Tricta F, Neumayr L, *et al.* Safety and efficacy of deferiprone for pantothenate kinase-associated neurodegeneration: a randomised, double-blind, controlled trial and an open-label extension study. Lancet Neurol 2019; 18:631–642.
18. Spaull RVV, Soo AKS, Hogarth P, *et al.* Towards precision therapies for inherited disorders of neurodegeneration with brain iron accumulation. Tremor Other Hyperkinet Mov (N Y) 2021; 11:51.
19. Abeti R, Baccaro A, Esteras N, Giunti P. Novel Nrf2-inducer prevents mitochondrial defects and oxidative stress in Friedreich's ataxia models. Front Cell Neurosci 2018; 12:188.
20. Lynch DR, Chin MP, Delatycki MB, *et al.* Safety and efficacy of omaveloxolone in Friedreich ataxia (MOXIe Study). Ann Neurol 2021; 89:212–225.
21. Lynch DR, Goldsberry A, Rummey C, *et al.* Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data. Ann Clin Transl Neurol 2023; 11:4–16.
22. Subramony SH, Lynch DL. A milestone in the treatment of ataxias: approval of omaveloxolone for Friedreich ataxia. Cerebellum 2023; 23:775–777.
23. Furqan M. Trofinetide-a new chapter in rett syndrome's treatment. Front Pharmacol 2023; 14:1284035.
24. ■■ Neul JL, Percy AK, Benke TA, *et al.* Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. Nat Med 2023; 29:1468–1475.

Building on findings in prior phase 2 studies, this randomized, double-blind, placebo controlled phase 3 study in female individuals with Rett syndrome established that treatment with the oral drug trofinetide, a synthetic analog of glycine–proline–glutamate, the N-terminal tripeptide of the insulin-like growth factor 1 protein, improved the co-primary endpoints, a least squares mean change from baseline to week 12 in the Rett syndrome Behavior Questionnaire and Clinical Global Impression, compared with placebo. Long-term benefit, including on Rett syndrome associated movement disorders, such as dystonia, remains to be investigated.

25. ■■ Saffari A, Brechmann B, Böger C, *et al.* High-content screening identifies a small molecule that restores AP-4-dependent protein trafficking in neuronal models of AP-4-associated hereditary spastic paraplegia. Nat Commun 2024; 15:584.

In this preclinical study, the investigators developed a high-throughput screening assay to identify molecules that correct aberrant protein trafficking in adaptor protein complex 4 deficiency, a rare but prototypical form of childhood-onset hereditary spastic paraplegia. Using this platform, an unbiased screen of 28 864 novel small molecules was conducted. Through a series of validation experiments, a lead compound BCH-HSP-C01 was identified. This approach highlights the potential of platform technologies, such as unbiased small molecule screens, to identify therapeutic targets for childhood-onset movement disorders.

26. ■■ Larasati YA, Savitsky M, Koval A, *et al.* Restoration of the GTPase activity and cellular interactions of Galpha(o) mutants by Zn(2+) in GNAO1 encephalopathy models. Sci Adv 2022; 8:eabn9350.

In this preclinical study, the investigators employed a high-throughput screening of approved drugs to zinc pyrithione and Zn2+ as agents restoring active conformation of GNAO1 GTPase activity. Dietary zinc improved motor function in a Drosophila melanogaster model of GNAO1-related disorder. This approach highlights the potential of drug repurposing screens for identifying therapeutic targets for childhood-onset movement disorders.

27. Holm A, Hansen SN, Klitgaard H, Kauppinen S. Clinical advances of RNA therapeutics for treatment of neurological and neuromuscular diseases. RNA Biol 2022; 19:594–608.
28. Silva AC, Lobo DD, Martins IM, *et al.* Antisense oligonucleotide therapeutics in neurodegenerative diseases: the case of polyglutamine disorders. Brain 2020; 143:407–429.
29. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, *et al.,* Phase 1–2a IONIS-HTTRx Study Site Teams. Targeting Huntingtin expression in patients with Huntington's Disease. N Engl J Med 2019; 380:2307–2316.
30. ■■ McColgan P, Thobhani A, Boak L, *et al.,* GENERATION HD1 Investigators. Tominersen in adults with manifest Huntington's disease. N Engl J Med 2023; 389:2203–2205.

This much awaited phase 3 study tested the nonallele-specific ASO, tominersen, designed to lower huntingtin levels in adults with Huntington's disease. Based on an overall benefit–risk assessment by an independent data monitoring commission, the trial was halted prematurely. An ad hoc analysis of the results at week 69 was carried out, showing that the mean composite UHDRS scores were worse compared with placebo in the every 8-week treatment group. No benefit was observed in the every 16-week treatment group.

31. Tabrizi SJ, Estevez-Fraga C, van Roon-Mom WMC, *et al.* Potential disease-modifying therapies for Huntington's disease: lessons learned and future opportunities. Lancet Neurol 2022; 21:645–658.
32. Kim J, Woo S, de Gusmao CM, *et al.* A framework for individualized splice-switching oligonucleotide therapy. Nature 2023; 619:828–836.
33. Muramatsu K, Muramatsu SI. Adeno-associated virus vector-based gene therapies for pediatric diseases. Pediatr Neonatol 2023; 64(Suppl 1):S3–S9.
34. Ling Q, Herstine JA, Bradbury A, Gray SJ. AAV-based in vivo gene therapy for neurological disorders. Nat Rev Drug Discov 2023; 22:789–806.
35. Mendell JR, Al-Zaidy SA, Rodino-Klapac LR, *et al.* Current clinical applications of in vivo gene therapy with AAVs. Mol Ther 2021; 29:464–488.
36. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. Nat Rev Drug Discov 2019; 18:358–378.
37. Kariyawasam D, Alexander IE, Kurian M, Farrar MA. Great expectations: virus-mediated gene therapy in neurological disorders. J Neurol Neurosurg Psychiatry 2020; 91:849–860.
38. Tanzler D, Kipping M, Lederer M, *et al.* Effects of theophylline on ADCY5 activation-From cellular studies to improved therapeutic options for ADCY5-related dyskinesia patients. PLoS One 2023; 18:e0282593.
39. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. Neurology 1993; 43:36–41.
40. Casaer P. Flunarizine in alternating hemiplegia in childhood. An international study in 12 children. Neuropediatrics 1987; 18:191–195.
41. Veenhuis SJG, van Os NJH, Janssen A, *et al.* Nicotinamide riboside improves ataxia scores and immunoglobulin levels in ataxia telangiectasia. Mov Disord 2021; 36:2951–2957.
42. Schuelke M, Mayatepek E, Inter M, *et al.* Treatment of ataxia in isolated vitamin E deficiency caused by alpha-tocopherol transfer protein deficiency. J Pediatr 1999; 134:240–244.
43. Amador MDM, Masingue M, Debs R, *et al.* Treatment with chenodeoxycholic acid in cerebrotendinous xanthomatosis: clinical, neurophysiological, and quantitative brain structural outcomes. J Inherit Metab Dis 2018; 41:799–807.
44. Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: long-term treatment response and prognosis. Neurology 1991; 41(2 (Pt 1)):174–181.
45. Lauxmann S, Sonnenberg L, Koch NA, *et al.* Therapeutic Potential of sodium channel blockers as a targeted therapy approach in KCNA1-associated episodic ataxia and a comprehensive review of the literature. Front Neurol 2021; 12:703970.
46. Strupp M, Zwergal A, Brandt T. Episodic ataxia type 2. Neurotherapeutics 2007; 4:267–273.
47. Strupp M, Kalla R, Dichgans M, *et al.* Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine. Neurology 2004; 62:1623–1625.
48. Stamelou M, Tuschl K, Chong WK, *et al.* Dystonia with brain manganese accumulation resulting from SLC30A10 mutations: a new treatable disorder. Mov Disord 2012; 27:1317–1322.
49. 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.
50. Alter AS, Engelstad K, Hinton VJ, *et al.* Long-term clinical course of Glut1 deficiency syndrome. J Child Neurol 2015; 30:160–169.
51. Kumar A, Szekely A, Jabbari B. Effective treatment of paroxysmal nonkinesigenic dyskinesia with oxcarbazepine. Clin Neuropharmacol 2016; 39:201–205.
52. Yeh TH, Lin JJ, Lai SC, *et al.* Familial paroxysmal nonkinesigenic dyskinesia: clinical and genetic analysis of a Taiwanese family. J Neurol Sci 2012; 323:80–84.
53. Sofou K, Dahlin M, Hallbook T, *et al.* Ketogenic diet in pyruvate dehydrogenase complex deficiency: short- and long-term outcomes. J Inherit Metab Dis 2017; 40:237–245.
54. Ortigoza-Escobar JD, Serrano M, Molero M, *et al.* Thiamine transporter-2 deficiency: outcome and treatment monitoring. Orphanet J Rare Dis 2014; 9:92.
55. Schilsky ML, Roberts EA, Bronstein JM, *et al.* A multidisciplinary approach to the diagnosis and management of Wilson disease: executive summary of the

2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases. Hepatology 2023; 77:1428–1455.
56. Rizzi S, Spagnoli C, Frattini D, *et al.* Clinical features in aromatic L-amino acid decarboxylase (AADC) deficiency: a systematic review. Behav Neurol 2022; 2022:2210555.
57. Lee NC, Chien YH, Hwu WL. A review of aromatic l-amino acid decarboxylase (AADC) deficiency in Taiwan. Am J Med Genet C Semin Med Genet 2019; 181:226–229.
58. Pearson TS, Gupta N, San Sebastian W, *et al.* Gene therapy for aromatic L-amino acid decarboxylase deficiency by MR-guided direct delivery of AAV2-AADC to midbrain dopaminergic neurons. Nat Commun 2021; 12:4251.
59. Tai CH, Lee NC, Chien YH, *et al.* Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. Mol Ther 2022; 30:509–518.
60. Francois-Heude MC, Poulen G, Flamand Roze E, *et al.* Intraputaminal gene delivery in two patients with aromatic L-amino acid decarboxylase deficiency. Mov Disord Clin Pract 2023; 10:811–818.
61. Keam SJ. Eladocagene exuparvovec: first approval. Drugs 2022; 82:1427–1432.
62. Simons CL, Hwu WL, Zhang R, *et al.* Long-term outcomes of eladocagene exuparvovec compared with standard of care in aromatic L-amino acid decarboxylase (AADC) deficiency: a modelling study. Adv Ther 2023; 40:5399–5414.
63. Chen X, Dong T, Hu Y, *et al.* Intrathecal AAV9/AP4M1 gene therapy for hereditary spastic paraplegia 50 shows safety and efficacy in preclinical studies. J Clin Invest 2023; 133:e164575.
64. Harris E. Sickle cell disease approvals include first CRISPR gene editing therapy. JAMA 2024; 331:280.
65. Aum DJ, Tierney TS. Deep brain stimulation: foundations and future trends. Front Biosci (Landmark Ed) 2018; 23:162–182.
66. Elkaim LM, Alotaibi NM, Sigal A, *et al.,* North American Pediatric DBS Collaboration. Deep brain stimulation for pediatric dystonia: a meta-analysis with individual participant data. Dev Med Child Neurol 2019; 61:49–56.
67. Cif L, Vasques X, Gonzalez V, *et al.* Long-term follow-up of DYT1 dystonia patients treated by deep brain stimulation: an open-label study. Mov Disord 2010; 25:289–299.
68. Decraene B, Smeets S, Remans D, *et al.* Deep brain stimulation for GNAO1-associated dystonia: a systematic review and meta-analysis. Neuromodulation 2023; S1094-7159(23)00938-8.
69. Rajan R, Garg K, Saini A, *et al.* GPi-DBS for KMT2B-associated dystonia: systematic review and meta-analysis. Mov Disord Clin Pract 2022; 9:31–37.
70. Straccia G, Reale C, Castellani M, *et al.* ACTB gene mutation in combined dystonia-deafness syndrome with parkinsonism: expanding the phenotype and highlighting the long-term GPi DBS outcome. Parkinsonism Relat Disord 2022; 104:3–6.
71. de Almeida Marcelino AL, Mainka T, Krause P, *et al.* Deep brain stimulation reduces (nocturnal) dyskinetic exacerbations in patients with ADCY5 mutation: a case series. J Neurol 2020; 267:3624–3631.
72. Ousingsawat J, Talbi K, Gomez-Martin H, *et al.* Broadening the clinical spectrum: molecular mechanisms and new phenotypes of ANO3-dystonia. Brain 2023.
73. Magrinelli F, Moualek D, Tazir M, *et al.* Heterozygous EIF2AK2 variant causes adolescence-onset generalized dystonia partially responsive to DBS. Mov Disord Clin Pract 2022; 9:268–271.
74. Mikati MA, Yehya A, Darwish H, *et al.* Deep brain stimulation as a mode of treatment of early onset pantothenate kinase-associated neurodegeneration. Eur J Paediatr Neurol 2009; 13:61–64.
75. Kosutzka Z, Tisch S, Bonnet C, *et al.* Long-term GPi-DBS improves motor features in myoclonus-dystonia and enhances social adjustment. Mov Disord 2019; 34:87–94.
76. Alonto AHD, Jamora RDG. A scoping review on the diagnosis and treatment of X-linked dystonia-parkinsonism. Parkinsonism Relat Disord 2023; 105949.
77. Krause P, Bruggemann N, Volzmann S, *et al.* Long-term effect on dystonia after pallidal deep brain stimulation (DBS) in three members of a family with a THAP1 mutation. J Neurol 2015; 262:2739–2744.
78. Zaman Z, Straka N, Pinto AL, *et al.* Deep brain stimulation for medically refractory status dystonicus in UBA5-related disorder. Mov Disord 2023; 38:1757–1759.
79. ■■ Vogt LM, Yan H, Santyr B, *et al.* Deep brain stimulation for refractory status dystonicus in children: multicenter case series and systematic review. Ann Neurol 2024; 95:156–173.
The role of deep brain stimulation in the treatment of pediatric cases of refractory status dystonicus remains to be defined. Taking a first step in this direction, the investigators retrospectively reviewed a case series and conducted a systematic review. Results support an overall benefit from GPi deep brain stimulation in the setting of refractory status dystonicus with reduced morbidity. This remains to be tested in prospective studies.
80. Lumsden DE. Neurosurgical management of elevated tone in childhood: interventions, indications and uncertainties. Arch Dis Child 2023; 108:703–708.
81. Lumsden DE, Cif L, Capuano A, Allen NM. The changing face of reported status dystonicus - a systematic review. Parkinsonism Relat Disord 2023; 112:105438.
82. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, *et al.* Efficacy and safety of deep brain stimulation in Tourette syndrome: the International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. JAMA Neurol 2018; 75:353–359.
83. Chou CY, Agin-Liebes J, Kuo SH. Emerging therapies and recent advances for Tourette syndrome. Heliyon 2023; 9:e12874.
84. Martino D, Deeb W, Jimenez-Shahed J, *et al.* The 5 pillars in Tourette syndrome deep brain stimulation patient selection: present and future. Neurology 2021; 96:664–676.
85. Yan H, Elkaim LM, Venetucci Gouveia F, *et al.* Deep brain stimulation for extreme behaviors associated with autism spectrum disorder converges on a common pathway: a systematic review and connectomic analysis. J Neurosurg 2022; 137:699–708.