DYSTONIA

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A narrative review: clinical trials in therapeutic interventions for dystonia (2020 - 2025)

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Dystonia is a disabling movement disorder affecting millions of people. Approach to managing this disorder in clinical practice include oral and intrathecal medication therapy, botulinum toxin injections, deep brain stimulation, rehabilitative regimens, or a combination of these. This paper is a comprehensive narrative journal review of the most recent clinical trials that were published or completed in the past 5 years or are ongoing (January 2020 to January 2025). The focus of this review it to discuss various treatment modalities and their respective outcome measure. The clinical trials described in this paper and their recent advancements are laying the foundation for future treatment trials.

KEYWORDS

review, dystonia, clinical trials, therapeutic, dystonia treatment

Introduction

As the third most common movement disorder [1], more than three million people worldwide suffer from this disabling diagnosis [2]. Dystonia is a complex movement disorder with no clinically available diagnostic laboratory or imaging tests. Therefore, identification of this disorder is based solely on clinical recognition of its phenomenology. The most recent updated definition in 2013 from the International Consensus Committee defined dystonia as:

> *"... a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation."* [3]

Dystonia phenomenologically can be described by two axes. Axis I focuses on clinical characteristics of dystonia; it describes age of onset, body distribution, temporal pattern and its associated features. Axis II focuses on etiology, further subdivided into nervous system pathology and whether it is acquired or inherited. Upwards of 30% of patients with idiopathic dystonia have reported having a family history of dystonia [4]. Inherited forms

TABLE 1 Movement Disorders Society Task Force recommendation for rating scales in dystonia [6].

Phenomenology	Recommended rating scale	Abbreviation
Blepharospasm	Blepharospasm Disability Index	BSDI
Cervical Dystonia	Cervical Dystonia Impact Scale	CDIP-58
	Toronto Western Spasmodic Torticollis Rating Scale	TWSTRS
Combined Craniocervical	Craniocervical Dystonia Questionnaire	CDQ-24
Laryngeal Dystonia	Voice Handicap Index	VHI
	Vocalized Performance Questionnaire	VPQ
Generalized Dystonia	Fahn-Marsden Dystonia Rating Scale	FMDRS/BFMDRS

of dystonia can be further subcategorized to isolated dystonia or combined dystonia as part of a neurologic syndrome (these include secondary dystonia, dystonia-plus syndrome, or a heredodegenerative disorder). Despite our expanded knowledge in characterizing this disorder, treatment remains largely targeted at symptomatic relief to improve posture and function. Current treatments utilized in clinical practice include oral and intrathecal medication therapy, botulinum toxin injections, deep brain stimulation, rehabilitative regimens, or a combination of these.

Therapeutic interventional clinical trials are crucial to advance the field. Designing the methodology for this clinically and etiologically heterogeneous movement disorder pose many challenges [5]. A mechanism-based approach requires further understanding of underlying pathophysiology and identification of factors that may impact disease progression. Meanwhile, a phenotypic approach focuses on improving dystonic symptoms by discovering new drugs or building upon existing therapies. Primary outcome measures through monitoring of treatment efficacy have been variable, relying mainly on patients' subjective reports of therapeutic benefit. Many study designs utilize rating scales for objective measures, but objective quantification continues to be challenging due to the heterogeneity of dystonia presentations. In 2013, the Movement Disorders Society (MDS) commissioned a task force to review and critique 36 potential rating scales, concluding with seven scales being recommended (see Table 1). These scales only apply to craniocervical, laryngeal and generalized dystonia. Rating scales fulfilling the suggested criteria encompass other subtypes of dystonia including the Jankovic Rating Scale (JRS), Blepharospasm Disability Scale, Functional Disability Questionnaire, Tsui Scale, Body Concept Scale, Oromandibular Dystonia Questionnaire, Unified Spasmodic Dysphonia Rating Scale (USDRS), Voice Handicap Index 10 (VHI-10), Voice-Related Quality of Life, Arm Dystonia Disability Scale (ADDS), Tubiana-Chamagne Score, Writer's Cramp Rating Scale (WCRS), Global Dystonia Rating Scale and Unified Dystonia Rating Scale (UDRS).

Therefore, this paper focuses on discussing treatment modalities explored and their respective outcome measures. This comprehensive narrative journal review aims to systematically outline the most recent clinical trials that were published or completed in the past 5 years or are ongoing in different dystonia presentations.

Methods

We reviewed the clinical trials from PubMed, ClinicalTrials.gov, Cochrane Library, Scopus, and Google Scholar through the National Institute of Health's Library. The searching strategy included clinical trials in dystonia and novel therapeutic interventions including medication, deep brain stimulation, transcranial magnetic stimulation, gene-targeted therapy, botulinum toxin therapy, and other emerging therapies. The search generated was filtered to include clinical trial publications, ongoing clinical trials, and recently completed clinical trials with conclusion dates between January 2020 and January 2025. Data extracted included history of the therapeutic intervention, study characteristics and trial methodology, primary and secondary outcomes. Case reports, case series, and retrospective cohort studies were excluded.

Medication therapy

The approach to medication treatment for dystonia explores its potential to shift from symptom management to targeted therapies driven by increased understanding in pathophysiology [7]. A deepening understanding of the role of neurotransmitters such as dopamine, acetylcholine, and GABA is leading to development of more specific therapeutic approaches (Table 2). Despite these advances, many medications remain off-label and side effects continue to be a concerning issue [8].

Dopaminergic and antidopaminergic therapies

Levodopa remains the cornerstone treatment for dopa-responsive dystonia, providing significant or complete

TABLE 2 Compilation of clinical trials with summary of oral and intrathecal medications studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Isolated Dystonia (Unspecified)	The AUDYT Trial: An Open-label Study to Define the Safety, Tolerability and Clinical Activity of Deutetrabenazine (AUstedo) in Adult Study Subjects with DYsTonia	University of Pennsylvania	Published abstract	NCT04173260	15	Proportion of participants tolerating maximum dose of 48 mg/day and complete the study at 3 months	6/ 15 patients (40%)
Secondary Dystonia (GNAO1 Disorder)	Prospective Pilot Trial to Address the Feasibility and Safety of Treatment with Oral Zinc in GNAO1 Associated Disorders	Children's University Hospital Cologne, Germany	Recruiting	NCT06412653	12	(1) Feasibility of daily treatment with oral zinc assessed by a diary over 6 months (2) Safety assessed through side effects, blood tests (3) Safety assessed by liver and pancreatic enzyme blood tests	N/A
Dystonic Cerebral Palsy	Pharmacogenomic Contributions to Trihexyphenidyl Biotransformation and Response in Children with Dystonic Cerebral Palsy (TRIKE2)	Children's Mercy Hospital Kansas City	Recruiting	NCT06554288	40	(1) Differences in pharmacokinetic parameters between CYP2D6 and CYP2C19 phenotype groups at baseline (2) Recruitment percentage, retention percentage, and dystonia efficacy measure completion	N/A
Dystonic Cerebral Palsy	PREDICT-ITB: Predicting Response in Children with Dystonic Cerebral Palsy to Intrathecal Baclofen	Baylor College of Medicine, Texas	Recruiting	NCT06606574	65	Changes in Barry-Albright Dystonia Scale scores at baseline, 3, 6, and 12 months	N/A
Blepharospasm	Exploratory Phase 2a Randomized, Double-blind, Placebo-controlled Study of Dipraglurant (ADX48621) Immediate Release Tablets in Patients with Blepharospasm	Addex Pharma S.A.	Published abstract	NCT05027997	15	(1) Adverse events (2) Computerized motor objective rater analysis (3) Analysis of blinking activity on wearable device	Dipraglurant was well-tolerated but did not provide any clinical benefit
Blepharospasm	Randomized Controlled Clinical Study on Wumeiwan Jiawei Fang Use in Patients with Blepharospasm	China Academy of Chinese Medical Sciences	Unknown	NCT05618470	80	(1) JRS (2) BDSI (3) Traditional Chinese Medicine syndrome scale (4) Treatment-related adverse events	N/A
Cervical Dystonia	Prospective, Open-label Clinical Study of Ingrezza (Valbenazine) for the Treatment of Cervical Dystonia	The Orthopedic Foundation, Ohio	Published abstract	NCT05157100	13	(1) Change in TWSTRS (2) Change in VAS for pulling	Significant differences at baseline and 12 weeks after (1) $p = 0.01$ (2) $p = 0.02$

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TABLE 2 (*Continued*) Compilation of clinical trials with summary of oral and intrathecal medications studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Cervical Dystonia	An Open-Label Phase 2a Study to Evaluate the Safety and Tolerability of Perampanel in Cervical Dystonia	Toronto Western Hospital	Published manuscript	NCT02131467	25	(1) Tolerability (ability to remain on any dose level of perampanel for the maintenance period) (2) Adverse events	(1) One tolerated 12 mg/day, 8 tolerated 2 mg/day (2) Median AEs per subject was 4; most common were dizziness, imbalance, falls. Most severe were dizziness, disorientation, worsening of cervical dystonia, irritability
Laryngeal Dystonia	Central Mechanisms and Treatment Response of Sodium Oxybate in Spasmodic Dysphonia and Voice Tremor	Massachusetts Eye and Ear Infirmary	Published manuscript	NCT03292458	106	Change from baseline symptom severity 40 min after drug intake (combined clinician-objective and patient-subjective VAS score)	Alcohol-responsive group had mean severity score 28.0 versus 14.2 for placebo ($p = 0.008$); no significant difference between alcohol-nonresponsive group and placebo

Recruiting: Study is actively enrolling patients. Published abstract: Brief results are published in a medical journal or at a conference. Published manuscript: Full manuscript published to peer-reviewed journal. Unknown: Last status update posted on clinicaltrials.gov has not been verified within 2 years.

symptom resolution in this condition that accounts for about 5% of childhood dystonias [9]. Early dopamine agonists such as apomorphine and bromocriptine showed promise in initial studies but are rarely used today due to limited efficacy and side effects [9]. Clozapine had moderate relief for segmental and generalized dystonias but required frequent monitoring for agranulocytosis [9]. Currently, there are no active clinical trials studying dopaminergic therapies in dystonia.

Anticholinergic medications

Trihexyphenidyl, an anticholinergic drug introduced in the 1950s, continues to be one of the most effective treatments for generalized dystonia [10]. However, side effects like confusion, dry mouth, and drowsiness often limit their use in adults, especially at higher doses. Other anticholinergics, such as benztropine and biperiden, are particularly effective in pediatric patients who can tolerate higher doses.

The Children's Mercy Hospital Kansas City has an actively recruiting trial, "Pharmacogenomic Contributions to Trihexyphenidyl Biotransformation and Response in Children with Dystonic Cerebral Palsy (TRIKE2)." [11] This Phase 1, 16-week, single-arm, nonrandomized pilot study is evaluating trihexyphenidyl metabolism in 40 pediatric patients. The primary endpoints focus on the influence of genetic factors, such as CYP2D6 and CYP2C19 genotypes, on the drug's pharmacokinetics. Outcomes include recruitment and retention percentages and completion rates of dystonia efficacy measures, to inform feasibility of future clinical trials.

GABA-targeting medications

Baclofen, a GABA-B receptor agonist, is effective in reducing spasticity and dystonia symptoms, particularly in childhood dystonia associated with spasticity. Intrathecal baclofen (ITB), introduced in 1991, is a standard intervention for severe cases unresponsive to oral medications. Benzodiazepines, such as diazepam and clonazepam, are considered second- or third-line options, particularly beneficial in myoclonus-dystonia. However, risks of sedation and dependence limit their long-term use. The PREDICT-ITB clinical trial, led by Baylor College of Medicine, aims to evaluate ITB's effects on children with dystonic cerebral palsy [12]. This interventional, single-group study will enroll 65 participants, through 2029. Over a 12-month period, participants will follow a standardized ITB titration protocol with four additional clinic visits to assess dystonia, spasticity, and function. The primary outcome measure is based on the Barry-Albright Dystonia Scale (BADS) at

baseline, 3-, 6- and 12-month after ITB initiation. The study aims to understand ITB's long-term effects, analyze brain injury patterns linked to dystonia outcomes, and develop a comprehensive measure of ITB efficacy in children with cerebral palsy. The study anticipates initiating recruitment soon.

The Massachusetts Eye and Ear Infirmary finished recruitment in 2024 for a clinical trial evaluating "Sodium Oxybate in Spasmodic Dysphonia and Voice Tremor," [13] enrolling participants with laryngeal dystonia (alcohol-responsive and alcohol-nonresponsive) with and without voice tremor. The randomized, placebo-controlled crossover trial enrolled 117 participants. Primary outcome measure compared recordings at baseline and 40 min after treatment intervention. This was assessed by both patient and clinician scores of symptom severity using the Visual Analog Scale (VAS) (0–100, higher scores indicating worse symptoms) along with dystonic voice break quantification by blinded clinician. Results were published in 2025, in which sodium oxybate significantly reduced symptom severity in alcohol-responsive laryngeal dystonia (mean VAS severity score 28.0 versus 14.2 for placebo ($p = 0.008$)) [14]. Meanwhile, there was no significant difference between the alcohol-nonresponsive group when compared to placebo. In addition, no significant difference was observed between the adductor and abductor laryngeal dystonia groups in response to sodium oxybate. Adverse events were mild to moderate: dizziness/lightheadedness (48%), daytime sleepiness (20%), and mild nausea (14%) without serious adverse events. This is the first controlled clinical trial demonstrating sodium oxybate as a therapeutic option for laryngeal dystonia and voice tremor, particularly for alcohol-responsive patients.

VMAT-2 inhibitors

VMAT-2 inhibitors represent a significant advancement in the management of tardive dystonia and dyskinesia with FDA approvals of valbenazine and deutetrabenazine FDA in 2017. From 2021 to 2023, a phase 4 open-label study by The Orthopedic Foundation assessed valbenazine for cervical dystonia [15]. Thirteen participants completed the study over 16 weeks with valbenazine titrated to 80 mg per day while maintaining botulinum toxin treatment. Primary outcome was measured by TWSTRS and VAS for pulling at 4 weeks before treatment and 12 weeks after. Patients also utilized wearable devices that collected data on involuntary movements. Preliminary abstract results reported significant improvements in outcome measures ($p = 0.01$ for TWSTRS, $p = 0.02$ for VAS) [16]. The manuscript with detailed results have not yet been published.

The University of Pennsylvania recently completed "An Open-label Study to Define the Safety, Tolerability and Clinical Activity of Deutetrabenazine (AUstedo) in Adult Study Subjects with DYsTonia (AUDYT)." [17] For this single-center, open-label study in adults with non-dopa responsive isolated dystonia, deutetrabenazine was titrated from 12 mg per day to a maximum of 48 mg per day over 12 weeks, followed by a one-week washout. Primary outcomes included the proportion of participants who reached their maximum tolerated dose (40%). Secondary outcomes assessed changes in dystonia severity (Global Dystonia Scale), suicidality (Columbia Suicide Severity Rating Scale), cognition (Mini Mental Scale), sleepiness (Stanford Sleepiness Scale), and parkinsonism (Unified Parkinson's Disease Rating Scale (UPDRS) Part III). Video evaluations of participants were reviewed by blinded raters. Out of the 15 enrolled patients, none suffered any serious adverse events. The most common non-serious adverse event was fatigue in 40% of the subjects. Although the median score change in the Global Dystonia Scale was 0, the variability was notably wide (−12 to 2 at the 3-month mark), suggesting a need for a larger cohort for a future clinical trial.

Glutamate targeting drugs

The results of "An Open-Label Phase 2a Study to Evaluate the Safety and Tolerability of Perampanel in Cervical Dystonia" were published in 2021 [18]. This study evaluated perampanel, an AMPA receptor antagonist in 25 participants with cervical dystonia. Only one participant reached the maximum dose (12 mg per day). Some participants tolerated lower doses (eight participants tolerated 2 mg per day). Most serious adverse event were dizziness, imbalance, worsening of cervical dystonia and irritability (one patient per event). Exploratory outcomes showed some improvements in pain relief (TWSTRS decrease by 3.2 points (95% confidence interval: −5.7 to −0.6, $p = 0.02$)) and sleep quality (improvement in CDIP-59 of 8.2 points (95% confidence interval: −14.5 to −2.0, $p = 0.01$)). Future studies should consider lower doses.

In 2021, Addex Pharma S.A. conducted a phase 2a randomized, double-blind, placebo-controlled trial evaluating the safety and tolerability of dipraglurant, a negative allosteric modulator of the mGlu5 receptor, for blepharospasm [19]. Fifteen participants were randomized to receive either 50 mg or 100 mg of dipraglurant or placebo. An additional primary outcome was the severity and frequency of blepharospasm using computerized motor evaluation by video analysis through a wearable device. A brief abstract was published reporting favorable tolerability of the drug, but no meaningful clinical benefit was observed. Further results have not yet been posted.

Additional pharmacological therapies

In 2024, the China Academy of Chinese Medical Sciences completed a Phase 2/3 trial evaluating the efficacy and safety of

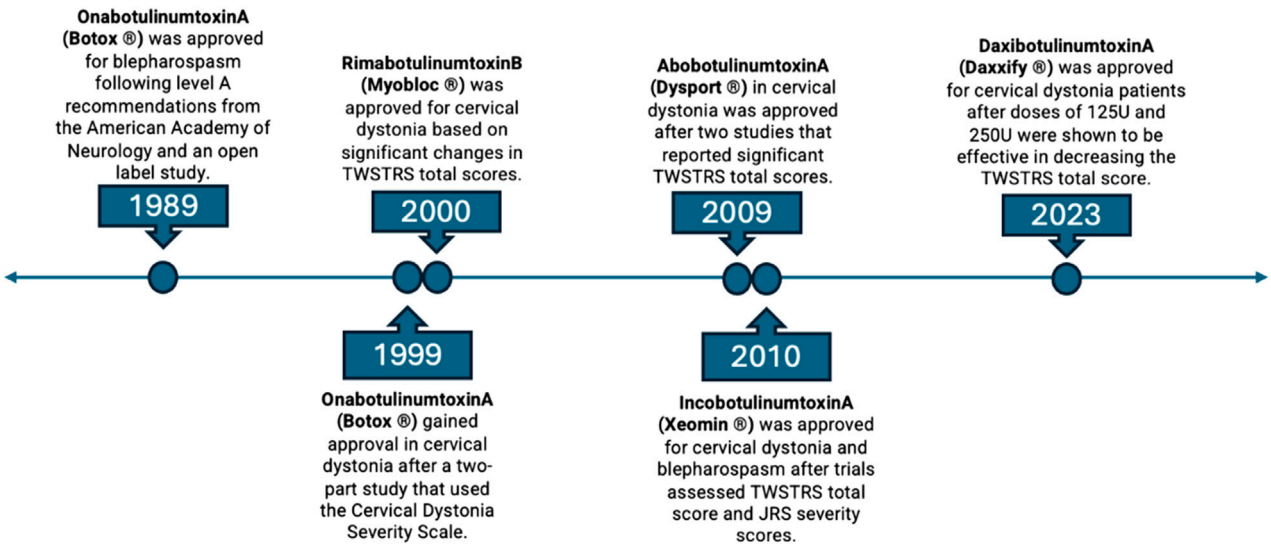

FIGURE 1
FDA approval timeline for botulinum toxins in different forms of dystonia [23].

Wu Mei Wan Jia Wei Fang, a traditional Chinese medicine, for idiopathic blepharospasm in 80 individuals [20]. This randomized controlled trial compared the traditional Chinese medication to one injection cycle of lanbotulinumtoxinA (Lantox), 2.5 units at four sites per eye. The primary outcome measure was change in the Jankovic Rating Scale (JRS), BSDI, Traditional Chinese Medicine syndrome scale, and treatment-related adverse events at 6 months. The results have not yet been posted.

The Children's University Hospital Cologne in Germany is studying, "The Prospective Pilot Trial to Address Feasibility and Safety of Oral Zinc in GNAO1 Associated Disorders." [21] Their goal is to investigate the safety and feasibility of daily zinc acetate dihydrate zinc for 6 months in 12 subjects with G Protein Subunit Alpha O1 (GNAO1) secondary dystonia. The primary outcome measures were assessed by patient documentation of their daily oral zinc intake, subjective safety assessment, and regular checks of liver and pancreatic enzymes. Three in-person assessments will include the Gross Motor Function Measure (GMFM-66), the BFMDRS and Abnormal Involuntary Movement Scale (AIMS). An exploratory outcome is zinc's therapeutic potential for all aspects of this rare condition. The study is actively recruiting.

Botulinum toxin therapy

In the 1980s, Drachman's experimental analysis of botulinum toxin (BoNT) on the hind limbs of chicks showed localized paralysis with no side effects [22]. These and further studies prompted the FDA approval of BoNT in 1989 for strabismus, blepharospasm, leg muscle spasm, and torticollis. BoNT is now widely for various muscle hyperactivity conditions; dystonia is one of its main therapeutic indications. Five commercially available BoNT formulations have FDA approval for first-line treatment of cervical dystonia (Figure 1); only two are approved for blepharospasm. Although cervical dystonia and blepharospasm are the only forms of dystonia with FDA approval, BoNT is routinely used in for other dystonia phenotypes (Table 3).

Craniofacial and cervical dystonia

DaxibotulinumtoxinA is the most recent type A BoNT to receive FDA-approval for cervical dystonia based on clinical trials conducted by Revance Therapeutics. DaxibotulinumtoxinA shares a similar mechanism of action with other BoNT formulations. However, its molecular size and unique stabilizing excipient peptide enhance binding through electrostatic charge and reduce spread of the toxin, leading to a longer therapeutic duration [24].

Revance completed two pivotal Phase 3 trials. "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Trial to Evaluate the Efficacy and Safety of a Single Treatment of DaxibotulinumtoxinA for Injection in Adults with Isolated Cervical Dystonia (ASPEN-1)" was completed in 2020, conducted at 60 sites internationally [25]. Patients with cervical

TABLE 3 Compilation of clinical trials with summary of botulinum toxin therapies studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Blepharospasm	Efficacy and Safety of Letibotulinum Toxin A for the Treatment of Essential Blepharospasm	Hugel Inc	Published abstract	NCT03641950	220	Change in JRS	Mean change in JRS score at week 4 showed significant reduction ($p < 0.0001$), confirming the non-inferiority
Cervical Dystonia	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Trial to Evaluate the Efficacy and Safety of a Single Treatment of DaxibotulinumtoxinA for Injection in Adults With Isolated Cervical Dystonia (ASPEN-1)	Revance Therapeutics, Inc.	Published manuscript	NCT03608397	291	TWSTRS (baseline to peak dose)	Improved TWSTRS compared to placebo (DAXI 125U: -8.5, $p < 0.0001$; DAXI 250U: -6.6, $p = 0.0006$)
Cervical Dystonia	A Phase 3, Open-Label, Multi-Center Trial to Evaluate the Long-Term Safety and Efficacy of Repeat Treatments of DaxibotulinumtoxinA for Injection in Adults With Isolated Cervical Dystonia (ASPEN-OLS)	Revance Therapeutics, Inc	Published abstract	NCT03617367	357	Treatment-emergent adverse events	Most common: dysphagia (mean 4.2% of 985 treatments), muscular weakness, and injection-site pain. Rate of adverse event remained stable or decreased after repeat dosing. No serious treatment-related TEAEs were reported
Cervical Dystonia	A Phase 2, Randomized, Double-Blind, Multicenter, Placebo Controlled Study to Evaluate the Safety and Efficacy of Intramuscular ABP-450 (prabotulinumtoxinA) Injection for the Treatment of Cervical Dystonia	AEON Biopharma, Inc	Published abstract	NCT04849988	57	Treatment-related serious adverse events (up to 20 weeks)	No serious adverse events occurred
Cervical Dystonia	An Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of Repeat Intramuscular ABP-450 (prabotulinumtoxinA) Injection for the Treatment of Cervical Dystonia	AEON Biopharma, Inc	Completed	NCT04871451	51	Treatment-related serious adverse events (up to 52 weeks)	No serious adverse events occurred
Cervical Dystonia	A 48-Week Prospective, Double-Blinded, Randomized, Cross-over Design in Multicenter Study of 250 Unit of Dysport Versus 50 Unit of Neuronox Injection for Cervical Dystonia in Thai Patients	Rajavithi Hospital	Published manuscript	NCT03805152	52	(1) TWSTRS (2) CDIP-58	(1) Both neubotulinumtoxinA and abobotulinumtoxinA groups had reduction in TWSTRS without significant difference between the two groups (2) CDIP-58 showed no significant difference compared to baseline and between the two groups

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TABLE 3 (*Continued*) Compilation of clinical trials with summary of botulinum toxin therapies studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Cervical Dystonia	24-Week Prospective, Double-Blinded, Randomized, Cross-over Design in Multicenter Study of 50 Unit of Neubotulinum Toxin Type A (Neuronox) and 100 Unit of Neubotulinum Toxin Type A (Neuronox) Injection for Cervical Dystonia in Thai Patients	Rajavithi Hospital	Completed	NCT04582929	50	(1) TWSTRS in a 24-week time frame (2) CDIP-58 in 24-week time frame	N/A
Cervical Dystonia	A Multi-center, Double-blind, Randomized, Parallel, Active-controlled, Phase I Clinical Trial to Compare the Safety and Efficacy of Botulax® Versus Botox® in Patients with Cervical Dystonia	Hugel Inc	Completed	NCT04171258	38	(1) Rate of Adverse Event (2) Change from Baseline in TWSTRS	N/A
Cervical Dystonia	An Open-Label, Non-Inferiority Study Evaluating the Efficacy and Safety of Two Injection Schedules of Xeomin® (incobotulinumtoxinA) [Short Flex Versus Long Flex] in Subjects with Cervical Dystonia With <10 Weeks of Benefit From OnabotulinumtoxinA Treatment	Merz Pharmaceuticals GmbH	Published manuscript	NCT01486264	207	Change from Baseline in TWSTRS	Significant improvements in TWSTRS with shorter interval injections demonstrating noninferiority
Cervical Dystonia	Comparison of Clinical and Kinematic Assessment in the Determination of Botox® Injection Parameters in Cervical Dystonia Patients	Western University, Canada	Published manuscript	NCT02662530	39	(1) TWSTRS Parts A and C (2) Participants with objective kinematic reductions in angular deviation and amplitude measures	Preliminary results from 28 patients showed comparable reduction in TWSTRS in both kinematic-guided and visual-guided groups though kinematic-guided group achieved reduction faster at 6 weeks
Laryngeal Dystonia	DaxibotulinumtoxinA Injection for Treatment of Adductor Spasmodic Dysphonia	University of California, San Francisco	Active, not recruiting	NCT05158166	20	Change in VHI-10 score baseline vs 6 weeks	N/A
Task-Specific Focal Hand Dystonia	A Placebo-Controlled, Double-Blind, Randomized, Cross Over Pilot Study of The Efficacy And Tolerability Of Incobotulinum Toxin A (Xeomin®) As A Treatment For Focal Task-Specific Dystonia Of The Musician's Hand	Icahn School of Medicine at Mount Sinai	Published manuscript	NCT02107261	19	Blinded Clinical Global Impression Scale and dystonia severity	Improvement in dystonia severity ($p = 0.04$) and overall musical performance ($p = 0.027$)

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TABLE 3 (*Continued*) Compilation of clinical trials with summary of botulinum toxin therapies studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Foot Dystonia in PD	Botulinum Toxin A (Onabotulinumtoxin A) for Foot Dystonia-associated Pain in Parkinson's Disease: A Randomized, Double-blind Placebo Control Study	University of Calgary	Published abstract	NCT04277247	33	(1) Change in King's PD pain scale (2) Change in Likert Visual Analogue Scale	Preliminary abstract showed 84% of participants with noted benefit
Foot Dystonia in PD	Evaluation of Therapeutic Benefits of Botulinum Toxin for Foot Dystonia associated with Parkinson's Disease	Suzhou Clinical Research Center	Published manuscript	JD-LJ-2021–002–01	25	(1) Modified Ashworth Spasm score (2) Visual analog pain score	(1) Reduced Modified Ashworth Spasm score for lower extremity dystonia at 3 weeks and 3 months ($p < 0.01$ for both) (2) Reduced pain associated with dystonia (3 weeks $p < 0.01$; 3 months $p = 0.005$)
Dystonic Tremor Syndrome	Factors Determining the Efficacy of Botulinum Toxin for Arm Tremor in Dystonia: An Exploratory Study	Radboud University Medical Center	Not yet recruiting	NCT06411028	60	TETRAS at 28 weeks	N/A

Not yet recruiting: Start date has begun, but no enrollment has occurred yet (anticipated to enroll soon). Active not recruiting: Completed enrollment, but study is still collecting data and following patients. Completed: Study completed enrollment and data collection and may or may not have posted results on clinicaltrials.gov. Published abstract: Brief results are published in a medical journal or at a conference. Published manuscript: Full manuscript published to peer-reviewed journal.

dystonia (excluding those with predominant retrocollis or anterocollis) and TWSTRS score of ≥20 were randomized into three groups: daxibotulinumtoxinA 125 units, daxibotulinumtoxinA 250 units, and placebo. The primary end point was the change in TWSTRS score from baseline at week 4–6. Among the 291 participants completing the study, the placebo group had a mean reduction of 4.3 in the TWSTRS total score compared to a mean reduction of 12.7 ($p < 0.0001$) in the 125U treatment group and 10.9 ($p = 0.0006$) in the 250U treatment group [22]. Significant improvements in the treatment groups were observed across all TWSTRS subcategories (severity, disability, and pain). In addition, the duration from time to injection to "loss of ≥80%" peak effect was significantly longer than that of other formulations of BoNTA, lasting 24 weeks and 20 weeks for the 125U and 250U groups, respectively. Notably, no dose-dependent increases in adverse events were observed, and most side effects were mild to moderate in severity. These findings suggest that daxibotulinumtoxinA offers a longer lasting and effective option for CD, potentially increasing the interval between treatments.

"A Phase 3, Open-Label, Multi-Center Trial to Evaluate the Long-Term Safety and Efficacy of Repeat Treatments of DaxibotulinumtoxinA for Injection in Adults with Isolated Cervical Dystonia (ASPEN-OLS)" was completed in 2021 [26]. It enrolled 271 patients from ASPEN-1 and 86 additional patients across 65 study centers with a 52-week follow-up. Results were published in an abstract. Successive injections of daxibotulinumtoxinA did not significantly increase in treatment-emergent adverse events such as dysphagia (ranging from 3.1%–4.7% after 4 cycles) indicating that successive treatments with daxibotulinumtoxinA is well-tolerated [27].

Other formulations of BoNT are undergoing clinical trials but have not yet been FDA approved for use in dystonia.

PrabotulinumtoxinA is FDA-approved for the treatment of glabellar lines. In 2018, prabotulinumtoxinA completed a two-year study in South Korea enrolling 234 patients to evaluate its efficacy and safety in treatment of essential blepharospasm, however, no results have yet been made available [28]. More recently, "A Phase 2, Randomized, Double-Blind, Multicenter, Placebo Controlled Study to Evaluate the Safety and Efficacy of Intramuscular ABP-450 (prabotulinumtoxinA) Injection for the Treatment of Cervical Dystonia" was conducted by AEON Biopharma, Inc [29]. Fifty-seven patients randomized to placebo, 150U, 250U or 350U completed the trial for the analysis. The primary outcome, treatment-related serious adverse events, was measured up to 20 weeks; none were reported. A notable secondary finding was that peak efficacy (regardless of dose) occurred early, within 2–8 weeks of treatment and wore off later, starting later at 16 weeks [30]. Fifty-one of the 57 patients, were enrolled in an extension study to follow treatment-related serious adverse events for up to 52 weeks; none were reported [31].

NeubotulinumtoxinA was developed in the early 2000s as a cost-effective alternative to onabotulinumtoxinA. It was

approved for blepharospasm and hemifacial spasm in South Korea in 2006 and since then, has been widely used for cosmetic and therapeutic purposes [32]. Starting in 2019, Rajavithi Hospital in Thailand conducted two clinical trials to study neubotulinumtoxinA in cervical dystonia. "A 48-Week Prospective, Double-Blinded, Randomized, Cross-over Design in Multicenter Study of 250 Unit of Dysport Versus 50 Unit of Neuronox Injection for Cervical Dystonia in Thai Patients" was a Phase 3 study completed in January 2021 [33]. The primary outcome assessed TWSTRS and CDIP-58 at initial 12 and 24 weeks and after treatment crossover at 12 and 24 weeks. Both groups showed significant reduction in total TWSTRS from baseline, without significant difference between the two groups. However, the TWSTRS disability score was decreased in only neubotulinumtoxinA group, while the TWSTRS pain subscale was only decreased in abobotulinumtoxinA group [34]. The CDIP-58 showed no significant difference compared to baseline or between the two groups. In this study there appeared to be comparable efficacy/non-inferiority between the two formulations. A second study comparing 50U and 100U of neubotulinumtoxinA was completed May 2021 [35]. Primary outcome measures were TWSTRS and CDIP-58. No results have yet been published.

LetibotulinumtoxinA is manufactured by Hugel Pharma in South Korea. It was found comparable in efficacy and safety to onabotulinumtoxinA in a 2017 study of post-stroke upper limb spasticity [36]. In 2020, a randomized controlled trial evaluated its efficacy in essential blepharospasm [37]. Across 15 sites, 220 participants completed the study. The mean reduction in the primary efficacy endpoint (JRS) at 4 weeks after treatment was significant, demonstrating non-inferiority. The full manuscript has not been published. Hugel Pharma then completed a clinical trial in 2021: "A Multi-center, Double-blind, Randomized, Parallel, Active-controlled, Phase I Clinical Trial to Compare the Safety and Efficacy of Botulax® Versus Botox® in Patients with Cervical Dystonia." [38] This study enrolled 38 patients with primary outcome of TWSTRS score change from baseline and rate of adverse events at 12 weeks. No results have been posted for this study.

In addition to new formulations of toxin, clinical trials are evaluating optimization of factors such as injection intervals for approved BoNTs. Comella et al. (2022) [39] assessed the efficacy and safety of incobotulinumtoxinA injections at two different intervals in cervical dystonia patients with early waning of benefit. This Phase 4, open label, randomized, noninferiority trial compared a shorter injection interval (8 ± 2 weeks) with a longer one (14 ± 2 weeks). After eight cycles of injections, the 207 subjects were evaluated at the 4-week mark. Both groups demonstrated significant improvements in TWSTRS with the shorter interval proving noninferior. The short interval group yielded slightly better outcomes with full analysis showing a mean difference of −1.3 ± 0.7 points ($p < 0.0001$). These findings highlight the flexibility and safety of tailoring injection schedules to individual patient needs, especially for patients with early treatment waning.

Other clinical trials are investigating the use of kinematics to understand dystonia response to treatment. The Western University in Canada studied the use of a kinematic measurement device to individualize onabotulinumtoxinA therapy. The Phase 2 trial, "Comparison of Clinical and Kinematic Assessment in the Determination of Botox® Injection Parameters in Cervical Dystonia Patients" compared using visual assessment to determine injection pattern versus a kinematic-determined injection pattern [40]. The kinematics group wore sensors to assess neck posturing dynamics in different axes at neutral position. This study enrolled 28 patients. The main difference reported was at week 6 in which the kinematic assessment group achieved a mean reduction of TWSTRS from 39.1 to 27.9 points while there was no significant reduction in TWSTRS in the visual assessment group [41]. At 38 weeks, both groups had comparable reduction in total TWSTRS (28.8%, −11.25 points in kinematics group versus 28.5%, −9.84 points in visual assessment group). Though both had comparable results long term, utilizing kinematic assessment may achieve faster reduction in dystonia symptoms after the first injection cycle than clinical judgment alone. The study was extended to enroll 39 patients, completing in January 2021. The updated results have not been published.

Laryngeal dystonia

There are currently no actively recruiting studies for botulinum toxin injections in laryngeal dystonia. The University of California, San Francisco anticipates evaluating "DaxibotulinumtoxinA Injection for Treatment of Adductor Spasmodic Dysphonia" in 20 patients as a Phase 1 and Phase 2 study [42]. The primary outcome will be to assess VHI-10 score peak benefit at 6 weeks compared to pre-treatment VHI-10 scores. This study is not recruiting yet.

Focal limb dystonia

Although not FDA-approved for limb dystonia, many BoNT formulations are used for symptomatic relief. Recent clinical trials have been focused on validating their efficacy, safety, and immunogenicity profile.

For upper limb dystonia, particularly task-specific musician dystonia, in 2024, the Icahn School of Medicine at Mount Sinai published their findings of "A Placebo-Controlled, Double-Blind, Randomized, Cross Over Pilot Study of The Efficacy and Tolerability Of Incobotulinum Toxin A (Xeomin®) As A Treatment For Focal Task-Specific Dystonia Of The Musician's Hand." [43] Nineteen participants completed the study. Each group received either placebo or

incobotulinumtoxinA initially with the option to receive a booster at week 2 and 4 for residual dystonia. After 12 weeks, the treatment and placebo groups crossed over. The primary outcome was change in dystonia rating at week 8 during peak dose effect compared to baseline. This study utilized experts blinded to both treatment group and treatment timing who scored musical performance videos and dystonia severity. The active treatment group had a significant improvement in video rating for dystonia severity ($p = 0.04$) and for overall musical performance ($p = 0.027$) [44]. This trial was especially valuable as double-blind trials of BoNT for musician's dystonia are rare. This study also utilized a novel approach to rate a focal limb dystonia in a clinical trial setting.

Lower limb dystonia, particularly that with lower limb pain in Parkinson's Disease (PD), significantly impacts quality of life and may not respond well to standard PD medications. The University of Calgary completed their study, "Botulinum Toxin A (OnabotulinumtoxinA) for Foot Dystonia-associated Pain in Parkinson's Disease: A Randomized, Double-blind Placebo Control Study" in December 2022 [45]. Thirty-three patients were randomized to receive either 100 units of onabotulinumtoxinA or placebo. Primary outcome was assessed at weeks 6 and 12 by change in King's Parkinson's disease pain scale score and in Likert Visual Analogue Scale. Patients were offered an open-label extension study with reassessment of primary outcome at 24 weeks. Preliminary data in an abstract in The Canadian Journal of Neurological Sciences in 2023 reported 84% of participants noting significant benefit, finding BoNT a safe and effective treatment option for pain relief from foot dystonia in Parkinson's Disease [46]. Final results have not been published yet.

Researchers at Suzhou Clinical Research Center also studied BoNT for foot dystonia in PD. Ni, et al. [47] recently published their study of 25 patients, finding a significant decrease in their primary outcome measures, Modified Ashworth Spasm Score and visual analog pain score at 3 weeks and 3 months. Four patients had minor adverse events that did not affect their walking ability. An instrumented plantar plate system was used to collect kinematic data on stressed area, stride width, stride length, gait velocity and balance in foot dystonia subjects. Distribution of plantar pressure changed (increased in the midfoot region when walking) as early as 3 weeks after BoNT treatment and was sustained at 3 months. Stride length also showed significant improvement. Thus, BoNT may improve pain, spasms and gait in the PD population presenting with foot dystonia.

Dystonic tremor syndrome

A new clinical trial from Radboud University Medical Center, "Factors Determining the Efficacy of Botulinum Toxin for Arm Tremor in Dystonia: An Exploratory Study" explores the efficacy of BoNT for dystonic tremor syndrome (DTS) in patients with upper extremity tremors and the difference in BoNT efficacy between dystonic tremor (DT) and tremor associated with dystonia (TAWD) in which tremor occurs in non-dystonic body parts [48]. This study will enroll 60 patients, 30 with DT and 30 with TAWD who will receive three BoNT sessions, once every 12 weeks. The primary outcome is tremor severity at 28 weeks, assessed using the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS). Secondarily, this study plans on exploring electrophysiological characteristics, cerebral circuitry activity, and musculoskeletal differences between the two groups. This study is not yet recruiting.

Surgical therapy

Deep brain stimulation

The first documented application of deep brain stimulation (DBS) for dystonia was reported in 1977 [49]. Since then, DBS, initially targeting the globus pallidus internus (GPi), has been extensively studied as a treatment for dystonia [50]. DBS was FDA-approved for dystonia in 2003 under the Humanitarian Device Exemption treatment-refractory primary dystonia [51]. Although the safety and efficacy of DBS have been validated across different types of dystonia (primary generalized dystonia, segmental dystonia, cervical dystonia, and DYT1 dystonia), methodologies and stimulation protocols have varied [52]. Many institutes have ongoing studies to follow long-term clinical outcomes in dystonia after DBS intervention [53–55]. Additionally, there are ongoing research to explore additional targets, particularly the subthalamic nucleus (STN) thalamus [56], or cerebellum [57], as well as to test novel stimulation methods such as biphasic stimulation [58] and intermittent theta burst DBS (Table 4) [59].

Generalized dystonia/hemidystonia

The University of Florida conducted a single center, double-blind, non-randomized crossover study in ten subjects with generalized dystonia ($n = 6$) or cervical dystonia ($n = 4$) [58]. Participants were randomized into active recharge biphasic stimulation or conventional stimulation. Primary outcomes were assessed with the UDRS, BFMDRS and TWSTRS four hours after stimulation. There was a significant reduction in UDRS in the biphasic stimulation group with mean change of −6.5 points compared to −0.3 points in the conventional stimulation group, $p < 0.04$; however, BFMDRS showed no difference. There was also no difference in TWSTRS for the four participants with cervical dystonia. The study established safety and tolerability of biphasic stimulation and suggested that the new stimulation paradigm might facilitate faster symptom relief for primary dystonia despite its limited sample size.

TABLE 4 Compilation of clinical trials with summary of surgical interventions studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Primary Dystonia (Unspecified)	Deep Brain Stimulation Effects in Dystonia: Time Course of Electrophysiological Changes in Treatment	University of Florida	Completed	NCT04568681	7	(1) UDRS (2) BFMDRS (3) TWSTRS	N/A
Primary Dystonia (Unspecified)	Subthalamic Nucleus Deep Brain Stimulation in Isolated Generalized or Segmental Dystonia: A Multicenter, Randomized, Double-blind, Sham-controlled, Parallel-group Trial	Ruijin Hospital, China	Unknown	NCT04650958	38	BFMDRS change from baseline to 3 months	N/A
Primary Dystonia (Unspecified)	Lessons from multitarget neurostimulation in isolated dystonia: Less is more?	Multicenter: Paris, Nantes, Bordeaux, Grenoble	Published manuscript	IDRCB2006-A00477-44	12	BFMDRS movement and disability scores among the GPI/STN/Cm-Pf monotherapy and GPI + STN/Cm-Pf combined therapy groups	44% improvement in GPI monotherapy group; no additional benefit with combined targets
Primary Dystonia (Unspecified)	Closed Loop Deep Brain Stimulation in Parkinson's Disease and Dystonia (Activa RC+S)	University of California, San Francisco	Active, not recruiting	NCT03582891	25	For dystonia patients (1) BFMDRS (2) TWSTRS (3) Karolinska Sleepiness Cale (4) Psychomotor vigilance task (5) Positive and Negative Affect Schedule	N/A
Primary Dystonia (Unspecified)	Dystonia Image-based Programming of Stimulation: A Prospective, Randomized, Double-blind Crossover Trial	Wuerzburg University Hospital, Germany	Recruiting	NCT05097001	80	BFMDRS or TWSTRS at 8 weeks	N/A
Primary Dystonia (Unspecified)	Double Blind, Nonrandomized Crossover Study of Active Recharge Biphasic Deep Brain Stimulation for Primary Dystonia	University of Florida	Published manuscript	NCT02468843	10	Change 4 h after stimulation: (1) TWSTRS for cervical dystonia and (2) UDRS and BFDMRS for generalized dystonia	After 4 h of biphasic DBS compared to conventional DBS: (1) No difference in TWSTRS (2) No difference in BFMDRS; significant decrease in UDRS (mean change −6.5 vs 0.3, $p < 0.04$)
Dystonia (Unspecified)	Clinical, Laboratory and Imaging Features, Treatment Trends and Long Term Outcomes of Patients Undergoing Lesioning Procedures for Movement Disorders - A Cohort Study and Registry	All India Institute of Medical Sciences, New Delhi	Not yet recruiting	NCT06352268	250	(1) BFMDRS - Disability scale (2) UPDRS	N/A

(Continued on following page)

TABLE 4 (*Continued*) Compilation of clinical trials with summary of surgical interventions studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Dystonia (Unspecified)	A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-Refractory Movement Disorders	Sunnybrook Health Sciences Centre & Toronto Western Hospital sponsored by Insightec	Unknown Status	NCT02252380	10	Severity of device & procedure-related complications	N/A
X-Linked Dystonia Parkinsonism	Bilateral Transcranial Magnetic Resonance-guided Focused Ultrasound Pallidothalamic Tractotomy for Patients With X-linked Dystonia-parkinsonism	University of the Philippines Manila	Available through Expanded Access	NCT05592028	28–70	Change in XDP-MDS of Philippines Scare scores	N/A
Hemidystonia	Multi-Target Pallidal and Thalamic Deep Brain Stimulation for Hemi-Dystonia	University of British Columbia	Unknown	NCT02982304	4	(1) BFMDRS (2) SF-36 (3) Adverse effects	N/A
Meige Syndrome	A Randomized Prospective Study Between STN-DBS and GPi-DBS in Meige Syndrome	Qilu Hospital of Shandong University, China	Recruiting	NCT06292559	100	Change in motor function and BFMDRS	N/A
Meige Syndrome	Deep Brain Stimulation and Pallidotomy in Primary Meige syndrome: a Prospective Cohort Study	Peking University People's Hospital, China	Published manuscript	NCT04618887	98	BFMDRS scores after one and 3 years compared to baseline	GPI improvement 61% (1y) and 65% (3y), STN improvement 66% (1y) and 71% (3y), pallidotomy improvement 58% (1y) and 50% (3y)
Cervical Dystonia	A Randomized Controlled Trial Comparing PAllidal and SubThalamic Deep Brain Stimulation for Cervical Dystonia (the PASTS-CD Study)	Chinese PLA General Hospital	Not yet recruiting	NCT05715138	98	(1) TWSTRS at 3, 6, 12 months (2) Tsui Scale at 3, 6, 12 months	N/A
Craniofacial Dystonia	Multicenter Evaluation of Deep Brain Stimulation for Idiopathic Craniofacial Dystonia: Globus Pallidus intErnus or Subthalamic Nucleus	Beijing Tiantan Hospital	Recruiting	NCT05416905	110	BFMDRS between two groups at 365 days	N/A
Laryngeal Dystonia	Deep Brain Stimulation for Laryngeal Dystonia: From Mechanism to Optimal Application	Indiana University	Recruiting	NCT05506085	12	(1) Change in total number of vocal fold movements via videoendoscopy (2) Change in acoustic voice recordings (3) Microelectrode recording during surgery	N/A

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TABLE 4 (*Continued*) Compilation of clinical trials with summary of surgical interventions studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Laryngeal Dystonia	Deep Brain Stimulation in Laryngeal Dystonia and Voice Tremor	Massachusetts Eye and Ear Infirmary	Recruiting	NCT05150093	120	(1) Intraoperative recordings of brain signals during speech production (2) Change in BFMDRS (3) Fahn-Tolosa-Marin Tremor Rating Scale	N/A
Task-Specific Focal Hand Dystonia	Deep Brain Stimulation Surgery for Treatment of Focal Hand Dystonia	National Institute of Neurological Disorders and Stroke (NINDS)	Active, not recruiting	NCT02911103	3	Adverse events in 5-year follow-up period to confirm safety of VOA/VOP thalamic DBS	N/A
Task-Specific Focal Dystonia	Phase 1 Clinical Trial for MR Guided Focused Ultrasound (FUS) Pallidotomy for the Treatment of Task Specific Focal Hand Dystonia (TSFD)	University of Maryland	Recruiting	NCT06367608	10	Incidence of treatment-related adverse events	N/A

Not yet recruiting: Start date has begun, but no enrollment has occurred yet (anticipated to enroll soon). Recruiting: Study is actively enrolling patients. Active not recruiting: Completed enrollment, but study is still collecting data and following patients. Available through expanded access: Results from initial cohort published and now offering therapeutic modality through longitudinal study. Completed: Study completed enrollment and data collection and may or may not have posted results on clinicaltrials.gov. Published manuscript: Full manuscript published to peer-reviewed journal. Unknown: Last status update posted on clinicaltrials.gov has not been verified within 2 years.

The Children's Hospital of Orange County conducted a small open-label pilot observational study utilizing intermittent theta-burst DBS in pediatric patients with secondary dystonia who underwent DBS implantation in various targets (GPi and thalamus) [59]. Based on a 3-point Likert scale ("better", "same", and "worse"), data was only recorded in results if clinicians, participants and parents reported the same effect. A subjective improvement in dystonic posturing was noted in 15 of the 19 subjects in the pallidum and five of the 12 subjects with thalamic leads. It was hypothesized that this intermittent cycling might desynchronize abnormal neuronal activity to restore normal function, but the study was limited by its lack of blinding for possible bias and its small sample size.

Ruijin Hospital recently completed an interventional clinical trial, "Subthalamic Nucleus Deep Brain Stimulation in Isolated Generalized or Segmental Dystonia: A Multicenter, Randomized, Double-blind, Sham-controlled, Parallel-group Trial" [60] evaluating the efficacy and safety of STN DBS as an alternative to GPi DBS in these populations. The primary outcome focused on the change from baseline at 3 months in the BFMDRS score in both sham and treatment groups. Secondary outcomes include motor and mental status, quality of life, and adverse events. The study started in January 2021 and was to complete by January 2022, however results are not yet available.

The University of British Columba completed a Phase 1 interventional clinical trial, "Multi-Target Pallidal and Thalamic Deep Brain Stimulation for Hemi-Dystonia" for patients who had insufficient benefit from GPi DBS [61]. Primary outcomes included the BFMDRS, SF-36 quality of life scale, and adverse effects of thalamic DBS monotherapy and thalamic/GPi combined therapy at 3 months. There are no results from this clinical trial yet published, however this trial followed an initial case report in which combined pallidal and thalamic DBS was more effective than single-target DBS, with 25% improvement in BFMDRS at 6-month follow-up [62].

A 2024 publication by Cuartero et al. [63] reported their prospective, randomized clinical trial to study the thalamic centromedian-parafascicular complex (Cm-Pf) as an alternative target in medically refractory dystonia patients. Twelve patients underwent dual DBS surgery implantation of GPI and one alternative target. This study compared GPi-, STN- or Cm-Pf-DBS monotherapy, and combined GPi/STN-DBS or GPi/Cm-Pf-DBS. Primary outcome measures were the BFMDRS disability and movement scores after each stimulation target was activated for 3 months. This study confirmed the efficacy and safety of GPi-DBS, with 44% improvement in dystonia severity at the 3-month mark. There was no additional benefit for dual-target stimulation or alternative target alone (STN and Cm-Pf). However, this study may have been insufficiently powered and 3 months may not have been sufficient to optimize stimulation parameters for a new target.

Craniofacial and cervical dystonia

The MEIGES trial ("Multicenter Evaluation of Deep Brain Stimulation for Idiopathic Craniofacial Dystonia: Globus Pallidus intErnus or Subthalamic Nucleus") led by Beijing Tiantan Hospital is currently enrolling 110 patients with idiopathic craniofacial dystonia [64]. The trial investigates whether STN-DBS is non-inferior to GPi-DBS in improving motor symptoms after 365 days. Primary outcome is the change in BFMDRS-motor score; secondary outcome measures include cognitive and quality-of-life measures. The study began in June 2022 and is actively recruiting.

Meige syndrome (isolated)

Qilu Hospital of Shandong University is also comparing STN DBS to GPi DBS in their clinical trial, "A Randomized Prospective Study Between STN-DBS and GPi-DBS in Meige Syndrome." [65] This study aims to enroll 100 patients with bilateral DBS implantation of either GPI or STN. Primary outcome will be the change in BFMDRS motor scores before DBS and at one, three, six, and 12 months after. Secondary outcome measures include questionnaires on health-related quality-of-life, sleep quality, and mental health. The study commenced in November 2023 and is expected to conclude in November 2025 recruitment is presently ongoing.

Peking University People's Hospital has published results of their clinical trial "A Comparative Study of GPI's DBS and Pallidotomy in the Treatment of Meige Syndrome." [66] This study assessed symptom improvement, complication rates, and quality of life after treatment. The primary outcome measure was BFMDRS scores after one and 3 years compared to baseline before surgery. Ninety-eight patients were enrolled. For GPi stimulation, BFMDRS mean improvement was 61% at 1 year and 65% at 3 years [67]. For STN stimulation, BFMDRS mean improvement was 66% at 1 year and 71% at 3 years. For pallidotomy, BFMDRS mean improvement was 58% at 1 year and 50% after 3 years. There were no significant differences between cohorts. However, the ability to adjust DBS parameters to maximize outcome, which is not possible after pallidotomy may be reflected when comparing the one-year to three-year benefit.

Cervical Dystonia

An upcoming trial conducted by the Chinese PLA General Hospital will compare the efficacy of GPi and STN DBS for treating cervical dystonia: "A Randomized Controlled Trial Comparing PAllidal and SubThalamic Deep Brain Stimulation for Cervical Dystonia (the PASTS-CD Study)." [68] The study aims to enroll 98 patients and will compare DBS targets with regard to symptom improvement, quality of life, cognitive effects, stimulation parameters, and adverse effects. Standardized video assessments and clinical evaluations will be obtained over one-year post-surgery. Primary outcome measures include the TWSTRS and Tsui Scale at three, six and 12 months. The trial is expected to be completed by November 2026 and has not yet started recruiting.

Laryngeal dystonia

Two clinical trials studying DBS in laryngeal dystonia are currently active. The study at Indiana University titled, "Deep Brain Stimulation for Laryngeal Dystonia: From Mechanism to Optimal Application," explores the effectiveness of GPi DBS for treating adductor laryngeal dystonia (ADLD) [69]. Enrolling 12 participants, the study will use three novel primary outcomes rather than classic rating scales for vocal cord disorders. This study will obtain acoustic voice recordings to measure voicing percentage and will quantify vocal fold movement through high-speed videoendoscopy. During surgery, beta and theta band power spectral density will be measured through microelectrode recording during phonation. This trial began in October 2022 and is expected to conclude by May 2025; they are actively recruiting.

An active study by the Massachusetts Eye and Ear Infirmary is recruiting 120 participants to examine "Deep Brain Stimulation in Laryngeal Dystonia and Voice Tremor" and to elucidate voice function's pathophysiological mechanisms in the basal ganglia-thalamo-cortical pathway [70]. The trial will utilize electrocorticography and subcortical activity recording during DBS surgery. Primary outcome measures are the correlation between brain signals and intraoperative speech production and changes in standard clinical outcomes using the BFMDRS and Fahn-Tolosa Marin Tremor rating scale. This study began in June 2022 and is expected to conclude by August 2026. They are actively recruiting.

Focal limb dystonia

The National Institute of Neurological Disorders and Stroke (NINDS) is currently working on a Phase 1/Phase 2 clinical trial, "Deep Brain Stimulation Surgery for Treatment of Focal Hand Dystonia" [71]. Five patients with severe, disabling focal hand dystonia who have inadequate response to BoNT treatment will be enrolled. The study seeks to confirm safety and explore DBS targeted at the thalamic ventralis oralis anterior and ventralis oralis posterior nuclear complex for this condition. The primary outcome measure is safety-the number and severity of adverse events in the five-year post-operative period. Secondary outcome measures include neuropsychological evaluation, clinical improvement using writer's and musician's cramp rating scales (BFMDRS, ADDS, Tubiana and Chamagne scale, WCRS), and BoNT dosage requirement at one and 5 years. The estimated completion date is February 2, 2029; this study is not currently recruiting.

Multiple dystonia phenotypes and innovative technology

A novel, "Closed Loop Deep Brain Stimulation in Parkinson's Disease and Dystonia" study at the University of

California, San Francisco has enrolled 25 patients, five of which are dystonia patients [72]. Primary outcome measures for dystonia include BFDMRS, TWSTRS, Karolinska Sleepiness Scale, a psychomotor vigilance task, and positive and negative affect schedule. The investigators formulate individualized adaptive DBS algorithms based on specific cortical biomarkers for each patient. Over the course of 8 weeks, each patient undergoes 4 weeks of open loop versus 4 weeks of adaptive mode DBS. This study may advance clinical practice in programming techniques to incorporate use of cortical biomarkers and decrease dependency on in-office programming. Although active, this study is no longer recruiting.

The "Dystonia Image-based Programming of Stimulation: A Prospective, Randomized, Double-blind Crossover Trial" [73] led by Wuerzburg University Hospital also evaluates the feasibility of novel image-guided programming for pallidal DBS in dystonia patients, comparing a computer-assisted DBS programming model against conventional clinician-based programming. Launched in 2021, the trial will enroll 80 participants with chronic DBS for isolated dystonia whose DBS settings and medications had remained stable for at least 3 months. Participants receive both clinician-guided and model-based DBS settings in a randomized sequence. The primary outcome is a responder analysis, comparing dystonia severity using BFMDRS or TWSTRS after 4 weeks of continuous stimulation for each setting. By utilizing individualized, image-based stimulation settings, this trial aims to optimize DBS programming, improve dystonia treatment outcomes, and significantly reduce non-responder rates, contributing to the future evolution of personalized DBS therapy. This study's primary completion date is anticipated to be September 2025, and it is still actively recruiting.

Brain lesioning/pallidotomy

Lesioning of bilateral GPi was one of the initial neurosurgical treatments explored for dystonia refractory to non-interventional therapies. After emergence of DBS, pallidotomy became less popular and less pursued. A systematic review in 2021 by Centen et al. [74] identified no randomized clinical trials of pallidotomy for dystonia and no long-term efficacy and safety data. With the literature on pallidotomy for dystonia being limited to case reports and case series, controlled trials would be needed to determine its role in the therapeutic landscape. There are recent studies re-exploring brain lesion in in clinical trials, using novel lesion in technology (Table 4).

A recently concluded interventional study sponsored by InSightec, "A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-Refractory Movement Disorders" [75] enrolled 10 patients. The primary outcome related to safety and evaluated device- and procedure-related complications over 12 months. The results of this study have not yet been posted.

The University of Maryland started its clinical trial, "Phase 1 Clinical Trial for MR Guided Focused Ultrasound (FUS) Pallidotomy for the Treatment of Task Specific Focal Hand Dystonia" [76] in 2024. This interventional study plans to enroll 10 patients with moderate to severe TSFD who failed response to BoNT and DBS. The primary safety outcome measure is the incidence of treatment-related adverse events for 6 months. Secondary outcome measures include change in dystonia severity (ADDS, WCRS, and musician's dystonia scores), SF-36 quality of life, and patient's Global Impression of Change. This study is projected to complete by June 2028 and is actively recruiting.

The University of the Philippines Manila is investigating lesioning effects of the pallidothalamic tract of patients with X-linked dystonia-parkinsonism (XDP) and confirmed DYT3 genetic mutation. This study, "Bilateral Transcranial Magnetic Resonance-guided Focused Ultrasound Pallidothalamic Tractotomy for Patients With X-linked Dystonia-Parkinsonism" [77] will target lesioning superior and medial to the medial subthalamic nucleus and lateral to the mamillo-thalamic tract. Primary outcome measure will be the change in the XDP-MDS of the Philippines Scale Scores before and after lesioning at 24 h, 2 weeks, and three-month intervals until 12 months. Other clinical data such as the BFMDRS, UPDRS Part III and adverse events will be collected. This study is planning to enroll 28–70 patients over 5 years [78], and is now in expanded access until 2026.

The All India Institute of Medical Sciences, New Delhi, is also studying surgical ablation in its "Clinical, Laboratory and Imaging Features, Treatment Trends and Long Term Outcomes of Patients Undergoing Lesioning Procedures for Movement Disorders - A Cohort Study and Registry." [79] This observational study plans to collect data from 250 patients with dystonia, tremor or PD. For dystonia, patients will be selected to undergo pallidal lesioning. The procedure can include radiofrequency, ultrasound-guided ablation or other lesioning techniques. The intervention cohort will be compared to the control group comprised of patients who were considered for, but did not undergo lesioning. The primary outcome measure will be long-term functional outcomes assessed by the BFMDRS disability subscale for dystonia and UPDRS for PD over a year. Additional data will be collected on demographics, clinical features, laboratory results, imaging features, and treatment trends. This study is projected to complete in December 2028; though it has not started recruiting yet, recruitment is anticipated soon.

Non-invasive brain stimulation

Transcranial magnetic stimulation

Transcranial Magnetic Stimulation (TMS) is non-invasive, using magnetic pulses to stimulate specific areas of the brain [80]. TMS is FDA-approved for the treatment of depression, chronic migraine, and obsessive-compulsive disorder [81], but not for dystonia. Despite some promising results for dystonia, variability in response, lack of optimized stimulation parameters [82, 83], and limited clinical trial data have hindered progression of TMS for dystonia to FDA approval (Table 5) [84].

Generalized dystonia

A double-blind, randomized placebo-controlled study at the AIIMS New Delhi Child Neurology Division investigated rTMS in children with generalized dystonia to determine whether it could modulate cortical excitability and improve motor control in 50 children aged 5–18 [85]. The primary endpoint was the BFDMRS-motor subscale at 12 weeks follow-up. The study also evaluated alterations in brain glucose metabolism using pre- and post-therapy 18F-FDG PET scans in a subset of patients and used fMRI to assess changes in brain activity following rTMS. Results have not yet been published.

Laryngeal dystonia

The Massachusetts General Hospital Institute of Health Professions has an ongoing study on the "Effects of Neuromodulation on Phonatory Function in Laryngeal Dystonia." [86] This masked study plans to enroll 25 patients randomized to a treatment or sham group. Both cohorts undergo baseline patient-reported assessments of voice production and TMS-measured neurophysiology. Each group then receives either active rTMS or sham session with interventional cross-over at 3 months. One primary outcome measure is objective assessment of phonatory function and voice quality through speech recording at day one, five and twelve. Another primary outcome measure is the change in cortical excitability to assess rTMS neurophysiological impact. This research could enhance understanding of neural mechanisms in laryngeal dystonia and support rTMS as a long-term treatment. This study is actively recruiting.

Cervical Dystonia

The University of Florida recently conducted two clinical trials focusing on combining TMS and BoNT treatment. The initial trial concluded in 2021 [87]; it sought to determine if adjunctive rTMS could prolong and increase effective symptom management in cervical dystonia by modulating cortical excitability in patients receiving BoNT. In this randomized, sham-controlled, masked study, participants received a one-week course of either rTMS or sham TMS, applied either two to 8 weeks before or after BoNT injection. The primary outcome measure was change in TWSTRS. At 12 weeks, the five patients in the treatment group had an absolute TWSTRS mean score of 13 ± 6 while the mean score for the four patients in the control group was 17 ± 8. No baseline values were posted yet. There were no serious adverse events. Following this study, the University of Florida completed a cross-over trial from 2022 to 2024, enrolling 5 patients: "Dystonia Treatment with Injections Supplemented by Transcranial Magnetic Stimulation (D-TWIST)." [88] This study applied 16 sessions of rTMS over four consecutive days beginning 9 weeks following the last BoNT injection. BoNT injections resumed at week 12. On the primary outcome, the TWSTRS scale, there were no significant differences between the treatment group (TWSTRS score 15.8 ± 4.78) and the control group (16.3 ± 4.41) 2 weeks after rTMS (p-value 0.691) [89].

Currently, Duke University in collaboration with the American Academy of Neurology is actively recruiting for their clinical trial, "Functional Magnetic Resonance Imaging (fMRI)-Guided Individualized Transcranial Magnetic Stimulation (TMS) for Cervical Dystonia." [90] The study started January 2025 and end in July 2029, enrolling 50 participants. This study is a masked, randomized single-arm crossover design comparing TMS at two different intensities. The primary outcome measure is the change in neck angles measured by a neck sensor device at baseline compared to 7 months. Functional MRI and behavioral assessments will measure TMS effects on brain activity and dystonic behavior. This study is actively recruiting.

Focal (including task-specific) and segmental limb dystonia

Task-specific focal dystonia, often experienced by musicians, occupations, or athletes who perform repetitive, precision-based tasks, is associated with decreased inhibition at multiple levels of the motor system. Approaches to restore inhibition to treat this condition are therefore being explored. Bhadran, et. al (2024) [91] conducted a randomized, crossover clinical trial targeting the inferior parietal lobule in 16 patients with task-specific focal hand dystonia. Patients were randomized into two groups: Each underwent a trial period, single session of 1 Hz rTMS or sham stimulation, had a washout period, then crossed over to the other intervention. The primary endpoint, the WCRS, was assessed immediately at the end of each session. Other measures included goniometry of joint angles, adverse event reporting, writing movement score and writing speed score. Notably, there was a significant difference in the change in WCRS between the sham and treatment sessions in each group (Group A−1.2, Group B 1.7, $p = 0.015$). This small cohort study indicates the potential utility of rTMS for treatment of focal hand dystonia.

Duke University also completed a study of rTMS for focal hand dystonia, "Development of Mechanistically Informed Therapy for Task-Specific Dystonia Using Noninvasive Neuromodulation." [92] Using 12 participants, they aimed to

TABLE 5 Compilation of clinical trials with summary of non-invasive stimulation studies in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Dystonia (Unspecified)	Towards Noninvasive Deep Brain Stimulation of the Basal Ganglia in Parkinson's Disease Using Low-intensity Transcranial Ultrasound Stimulation	University Health Network, Toronto	Active, not recruiting	NCT06232629	10	(1) Adverse events (2) Local field potential changes	N/A
Generalized Dystonia	Effect of Repetitive Transcranial Magnetic Stimulation in Children with Generalized Dystonia	AIIMS New Delhi Child Neurology Division	Unknown Status	CTRI/2022/01/039806	10	BFMDRS - Motor score	N/A
Cervical Dystonia	Combined Therapy With rTMS and Botulinum Toxin in Primary Cervical Dystonia	University of Florida	Completed	NCT02542839	9	TWSTRS	Post-stimulation TWSTRS in treatment group: 13 ± 6; control group: 17 ± 8
Cervical Dystonia	Dystonia Treatment with Injections Supplemented By Transcranial Magnetic Stimulation	University of Florida	Published abstract	NCT04916444	5	TWSTRS	No significant difference between treatment and control after 2 weeks of rTMS
Cervical Dystonia	Functional Magnetic Resonance Imaging (fMRI)-Guided Individualized Transcranial Magnetic Stimulation (TMS) for Cervical Dystonia	Duke University	Recruiting	NCT06328114	50	Changes in neck angles measured by sensor device	N/A
Cervical Dystonia	Transcranial Electrical Stimulation (tES) for the Treatment of Cervical Dystonia	University of Colorado, Denver	Completed	NCT03369613	36	(1) Alterations in brain functional connectivity between pallidum and putamen (2) TWSTRS	N/A
Laryngeal Dystonia	The Effects of Neuromodulation on Phonatory Function in Laryngeal Dystonia	MGH Institute of Health Professions	Recruiting	NCT05095740	25	(1) Change of phonatory function/ cepstral peak prominence (2) Change in cortical excitability via cortical silent period	N/A
Task-Specific Focal Hand Dystonia	Repetitive Transcranial Magnetic Stimulation to the Inferior Parietal Lobule in Task-Specific Focal Hand Dystonia: a Randomized, Sham control, Double Blind, Crossover Study	AIIMS New Delhi	Published Manuscript	CTRI/2020/01/022738	16	WCRS	Significant improvement after real stimulation, WCRS difference real minus sham mean (SD): −1 (1.3), 95% CI: (−2, −1), p = 0.002
Task-Specific Focal Hand Dystonia	Development of Mechanistically Informed Therapy for Task-Specific Dystonia Using Noninvasive Neuromodulation	Duke University	Completed	NCT06422104	12	Number of participants who complete the study to predict feasibility of TMS during writing task	N/A

(Continued on following page)

TABLE 5 (*Continued*) Compilation of clinical trials with summary of non-invasive stimulation studies in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Task-Specific Focal Hand Dystonia	Duke Accelerated Transcranial Magnetic Stimulation for Focal Hand Dystonia	Duke University	Recruiting	NCT06015672	20	(1) Change in behavioral writing measure (2) Change in brain connectivity in motor network using fMRI	N/A

Recruiting: Study is actively enrolling patients. Active not recruiting: Completed enrollment, but study is still collecting data and following patients. Completed: Study completed enrollment and data collection and may or may not have posted results on clinicaltrials.gov. Published abstract: Brief results are published in a medical journal or at a conference. Published manuscript: Full manuscript published to peer-reviewed journal. Unknown: Last status update posted on clinicaltrials.gov has not been verified within 2 years.

identify whether premotor cortex or primary somatosensory cortex might be a better rTMS target, comparing each to sham rTMS, by receiving one session to each target with 1 week washout in between. Response was measured by analysis of writing on a sensor tablet, examiner and patient dystonia rating scales and functional MRI scans. Results have not yet been published. However, a subsequent clinical trial, "Accelerated TMS for Focal Hand Dystonia" [93] referenced this study, mentioning improvement of symptoms after one session (though target efficacy was not specified). This trial is still actively recruiting.

Transcranial electrical stimulation

Another stimulation technique recently studied is transcranial electrical stimulation (tES). The University of Colorado completed Phase 1 and Phase 2 trials in 2021 to investigate the effects of tES in cervical dystonia patients in a double blind, randomized parallel assignment [94] with cessation of BoNT therapy for at least 10 weeks. Phase 1 compared healthy controls and cervical dystonia group by obtaining a 60-min MRI while tES and sham tES are given in randomized blocks. The primary outcome was a change in mean functional connectivity between pallidum and putamen during this session. Phase 2 of this study enrolled only cervical dystonia patients, aiming to assess whether tES could modulate brain connectivity and improve clinical symptoms over five consecutive days of 20-minute tES compared to sham tES. The primary outcome was improvement in TWSTRS. This clinical trial's results have not been published (Table 5).

Transcranial ultrasound stimulation

An emerging therapeutic modality for dystonia is being studied by the University Health Network, Toronto utilizing transcranial ultrasound stimulation (TUS): "Towards Non-Invasive Deep Brain Stimulation of the Basal Ganglia in Parkinson's Disease Using Low-intensity Transcranial Ultrasound Stimulation." [95] This study enrolled ten patients with Parkinson's Disease and dystonia who previously had a DBS model with sensors that can monitor local field potentials to correlate to hyperkinetic and hypokinetic movements. The participants will have their DBS stimulation turned off, but sensors remain on while they undergo two TUS stimulation protocols or sham. The two TUS modalities for the treatment group are: 5 Hz for two minutes to increase cortical excitability and 10 Hz for 40 s to inhibit motor cortical activity, 1 week apart, to bilateral GPi. The primary endpoint is to evaluate any treatment-related adverse events of TUS. Another primary endpoint will focus on any changes in the amplitude of local field potential power spectrums recorded from the DBS leads across different frequencies (beta, alpha, theta) during a 4-minute-long recording at baseline and during the session. This study is active (Table 5).

Gene-targeted therapies

Hereditary dystonias are linked to several genes, including pathogenic variations of VPS16, TOR1A, THAP1, GNAL, and ANO3 [4]. To date, there is no FDA-approved gene-targeted therapy for any isolated hereditary dystonia. However, *in vitro* studies are exploring potential genetic therapeutic interventions for a common hereditary form of childhood and adolescent-onset dystonia: DYT1 [96]. DYT1 is caused by a mutation in the TorsinA (TOR1A) gene on chromosome 9q34 from a trinucleotide GAG deletion. This deletion results in mutated TorsinA, which is hypothesized to reduce ATPase activity. Cruz et al. selectively engineered an RNA-guided endonuclease from *Streptococcus* pyogenese, CRISPR-Cas9, to disrupt the C-terminal region of mutated TorsinA in fibroblasts. Results showed selective reduction of TorsinA protein levels in Cas9-edited DYT1 fibroblasts with phenotypic recovery similar to that of control fibroblasts, potentially indicating return of wild-type TorsinA normal function. There are currently no active clinical trials testing this or other gene-targeted therapy in patients with

hereditary dystonia. However, many of the ongoing clinical studies for hereditary dystonias are focused on understanding their natural history and phenotype for clinical trial readiness (Table 6) [97–99].

Combined dystonia

Aromatic L-amino acid decarboxylase (AADC) deficiency, a rare genetic condition that causes complex movement disorder and cognitive behavioral impairment, has been of interest the past few years. More than 90% of this population presents with a movement disorder, especially dystonia of the eye muscles resulting in oculogyric crises with or without involvement of limbs and whole-body dystonic posturing [100].

In November 2024, FDA approved the first gene therapy for AADC deficiency based on positive result from phase1/2 clinical trials [101]. In 2022, the National Taiwan University Hospital recently completed "A Phase I/II Clinical Trial for Treatment of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC" [102], its expansion study [103], and a compassionate use trial. These trials utilized adeno-associated virus serotype 2 driven by human vectors (AAV2-hAADC) to deliver gene therapy (eladocagene exuparvovec) via direct intraputaminal infusions bilaterally. Though patients were followed for 5 years, their primary outcome measures at one-

TABLE 6 Compilation of clinical trials with summary of gene-targeted therapies in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Isolated Dystonia	Dystonia Genotype-Phenotype Correlation	University of Texas	Recruiting	NCT03428009	200	(1) Structural and functional imaging (2) Genetic Analysis	N/A
Combined Dystonia	Natural History of ATP1A3-related Disease: A Deep Phenotyping-genotyping Project	Institute of Child Health	Unknown	NCT03857607	100	Disease progression	N/A
Combined Dystonia	Database Of Clinical Data for Individuals with Variants in The IRF2BPL Gene	Children's Hospital Medical Center, Cincinnati	Completed	NCT03892798	34	Questionnaire: age at development of symptoms and diagnosis, method for diagnosis, specific mutations detected, additional complications with treatment	N/A
Combined Dystonia	A Clinical Trial for Treatment of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC	National Taiwan University Hospital	Published manuscript	NCT02926066, NCT01395641	26	(1) PDMS-2 (2) CSF metabolites (HVA and 5-HIAA)	(1) Mean PDSM-2 increase 10.4 to 80.5 ($p < 0.01$) at 1 year (2) Mean HVA increase 6.6 to 30.2 nmol/L ($p < 0.001$), no difference in 5-HIAA levels
Combined Dystonia	Single-Stage, Open-Label, Safety and Efficacy Study of Adeno-Associated Virus Encoding Human Aromatic L-Amino Acid Decarboxylase by Magnetic Resonance MR-guided Infusion into Midbrain in Pediatric Patients With AADC Deficiency	Ohio State University and UCSF Children's Hospital	Recruiting	NCT02852213	42	(1) Adverse events (2) CSF HVA, 5-HIAA, 3-OMD	N/A

Recruiting: Study is actively enrolling patients. Completed: Study completed enrollment and data collection and may or may not have posted results on clinicaltrials.gov. Published manuscript: Full manuscript published to peer-reviewed journal. Unknown: Last status update posted on clinicaltrials.gov has not been verified within 2 years.

year post-surgery included the Peabody Developmental Motor Scales-2 (PDSM-2) and measurement of cerebrospinal fluid (CSF) metabolites homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) compared to baseline. In the 26 patients, PDSM-2 mean score increased from 10.4 to 80.5 ($p < 0.01$). Mean CSF HVA levels also increased from 6.6 to 30.2 nmol/L ($p < 0.001$) though CSF 5-HIAA showed no difference [104]. There was also evidence of increased dopamine production through PET imaging with L-6-[^{18}F] fluoro-3, 4-dihydroxyphenylalanine tracer. This study demonstrated long term safety and efficacy of eladocagene exuparvovec gene therapy.

Another group at Ohio State University in conjunction with the University of California San Francisco Benioff Children's Hospital recently published preliminary results from their study, "Single-Stage, Open-Label, Safety and Efficacy Study of Adeno-Associated Virus Encoding Human Aromatic L-Amino Acid Decarboxylase by Magnetic Resonance MR-guided Infusion into Midbrain in Pediatric Patients with AADC Deficiency." [105] Primary outcome measures included adverse events related to surgery and gene transfer as well as CSF metabolite concentrations (HVA, 5-HIAA, and 3-O-methyldopa (3-OMD)). Secondary outcomes included a gross motor function measure, symptom diary and a fluorodopa PET scan. Notably, in all 7 subjects reported so far, oculogyric crises log of duration and severity improved from 2 months before surgery compared to the 24-month follow-up period [106]. Oculogyric crises ceased in 6 out of 7 subjects within 90 days. The 7th subject had residual episodes, but they were significantly reduced in severity. The clinical benefits were attributed to the physiological restoration of dopamine pathways in midbrain neurons. This study provides a framework for consideration of similar treatment of other genetic diseases of the central nervous system with developing application of MRI technology to safely deliver gene therapy. This trial is still actively recruiting with the goal to enroll 42 participants (Table 6).

Other therapeutic interventions

Many other therapeutic interventions have been explored in small cohort studies or case series with variable therapeutic responses. Therefore, a wide array of these emerging therapies is being studied in a formal clinical trial setting (Table 7).

Vibrotactile/vibration muscle therapy

Vibration muscle stimulation (VMS) and vibrotactile stimulation (VTS) are non-invasive neuromodulation techniques that differ in their mechanisms, applications, and therapeutic goals. VMS directly stimulates muscles, activating sensory receptors that influence proprioception, muscle tone, and pain perception [107]. It is primarily used in rehabilitation settings for movement disorders like cervical dystonia, where it helps reduce muscle stiffness, improve motor function, and alleviate pain when combined with physiotherapy. In contrast, VTS targets sensory processing by stimulating cutaneous mechanoreceptors through skin-applied vibrations [108]. It is commonly used for laryngeal dystonia [109]. Applied to the skin overlying the larynx, VTS can enhance speech fluency, reduce vocal strain, and minimize voice breaks [110]. Unlike VMS, which is integrated into structured physical therapy programs, VTS is often used at-home and as a potential alternative or adjunct to other treatments such as voice therapy and BoNT injections [111].

Vibration muscle stimulation in cervical dystonia

The VIBRA-DYSTONIA trial, conducted by Fondazione Don Carlo Gnocchi Onlus, investigates the role of VMS in reducing pain and improving quality of life for patients with primary cervical dystonia [112]. This masked study focuses on patients who received BoNT within 30 days and are undergoing an integrated rehabilitation program including physiotherapy and occupational therapy. Launched in 2022, this trial aims to enroll 28 participants, randomly assigned to either a therapeutic VMS group (80 Hz, 0.5 mm vibration amplitude) or a sham VMS group that receives no actual vibration. Both groups participate in a 10-session rehabilitation program, including 45 min of physiotherapy, 15 min of VMS (or sham), and 30 min of occupational therapy. The study's primary outcome measures assess pain and disability using the TWSTRS and the McGill Pain Questionnaire, while secondary outcomes focus on dystonia severity, measured by the Tsui Score. Participants undergo evaluations at baseline, mid-treatment, and post-treatment. If successful, this trial could show VMS to be a potentially valuable adjunct to rehabilitation programs for cervical dystonia, offering a non-invasive approach to pain management and functional improvement. Though active until July 2027, this study is not currently recruiting (Table 7).

Vibrotactile stimulation in laryngeal and cervical dystonia

Vibrotactile stimulation for laryngeal dystonia has evolved significantly over the years, with multiple studies refining treatment parameters, usability, and long-term viability as an alternative or adjunctive treatment to BoNT injections. Since 2019, researchers have examined VTS's impact on voice quality, at-home usability, and neuromodulation potential, leading to a progressive expansion of its applications.

The first clinical trial to systematically investigate VTS in laryngeal dystonia, conducted by the University of Minnesota from 2019 to 2022 [113], focused on evaluating its effects on voice quality in adductor laryngeal dystonia patients. This randomized trial analyzed data from 39 participants, randomized into 40 Hz or 100 Hz VTS treatment groups over 11 weeks. Patients were assessed acutely with a 20-min

TABLE 7 Compilation of clinical trials with summary of other treatment modalities studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Dystonia (Unspecified)	Exercise Training in Dystonia and Other Involuntary Movement Disorders	University of Florida	Completed	NCT03318120	11	(1) TWSTRS (2) BFMDRS	N/A
Dystonia (Unspecified)	Progressive Resistance Exercise and Dystonia Pathophysiology	University of Florida	Recruiting	NCT05663840	56	(1) fMRI signals (2) TMS motor cortex excitability and plasticity	N/A
Cervical Dystonia	Efficacy of Segmental Muscle Vibration on Pain Modulation in Patients with Primary Cervical Dystonia: a Randomized Controlled Study	Fondazione Don Carlo Gnocchi Onlus, Italy	Active, not recruiting	NCT06748846	28	(1) TWSTRS (2) McGill Pain Questionnaire	N/A
Cervical Dystonia	Evaluation of the Effect of Personalized Exercise Program on Clinical Findings and Quality of Life of Patients with Cervical Dystonia Who Received Botulinum Toxin Type a Injection	Ankara University	Recruiting	NCT05502718	34	TWSTRS-Pain (1–20)	N/A
Cervical Dystonia	Relief of Pain in Patients with Cervical Dystonia Through the Use of Sensory Threshold TENS	Central Hospital, Nancy, France	Published manuscript	NCT04949594	40	TWSTRS	-8-point change from baseline (±4.62, p = 0.0001)
Cervical Dystonia	The Effects of Vibrotactile Stimulation (Not Impossible Vibrohealth) on Motor Control and Symptoms in Patients with Movement Disorders	University of Florida	Completed	NCT05106816	40	(1) TWSTRS (2) CGI-I	N/A
Laryngeal Dystonia	Laryngeal Vibration as a Non-invasive Treatment for Spasmodic Dysphonia	University of Minnesota	Completed	NCT03746509	42	Voice assessment with cepstral peak prominence measures	Voice quality decay within 30 min, no conclusive evidence for long-lasting benefit
Laryngeal Dystonia	Usability of Laryngeal Vibro-tactile Stimulation as a Non-invasive Treatment for the Voice Disorder Spasmodic Dysphonia	University of Minnesota	Completed	NCT06111027	32	Perceived vocal effort (0–10 scale)	N/A
Laryngeal Dystonia	Laryngeal Vibro-tactile Stimulation as a Non-invasive Symptomatic Treatment for Spasmodic Dysphonia	University of Minnesota	Not yet recruiting	NCT05467228	60	Change in perceived speech effort, smoothed cepstral peak prominence, and speech quality vector	N/A
Laryngeal Dystonia	Adaptive Closed-loop Brain-computer Interface Therapeutic Intervention in Laryngeal Dystonia	Massachusetts Eye and Ear Infirmary	Recruiting	NCT04421365	40	Perceptual voice analysis for change in dystonic voice breaks	N/A

(Continued on following page)

TABLE 7 (*Continued*) Compilation of clinical trials with summary of other treatment modalities studied in dystonia the past 5 years.

Condition	Trial name	Institution	Status	Clinical trial ID	Number of participants	Primary outcome measure	Results (if posted or published)
Task-Specific Focal Dystonia	Treatment Effect and Relevance on Daily Life of a Video-supervised Sensorimotor Training Program and Its Influence on the Pathophysiology in Writer's Cramp	University Hospital Schleswig-Holstein	Recruiting	NCT04611009	54	Canadian Occupational Performance Measure	N/A
Truncal Dystonia in PD	Osteopathic Manual Treatment of Postural Abnormality, Pain, and Autonomic Control of Cardiac Function in People with Parkinson's Disease and Truncal Dystonia	New York Institute of Technology	Completed	NCT03307161	10	Change in posture and heart rate variability	N/A

Not yet recruiting: Start date has begun, but no enrollment has occurred yet (anticipated to enroll soon). Recruiting: Study is actively enrolling patients. Active not recruiting: Completed enrollment, but study is still collecting data and following patients. Completed: Study completed enrollment and data collection and may or may not have posted results on clinicaltrials.gov. Published manuscript: Full manuscript published to peer-reviewed journal.

application of VTS and then given repeated session VTS at home, once or three times per week, for 3 months. The primary outcomes measure, voice quality using smoothed cepstral peak prominence, was assessed at weeks one, six and 11. About a third of the patients showed improvement in voice quality. Notably in the acute setting, meaningful improvement of at least 30% occurred within 15–20 min. This effect was not long-lasting, however, as voice quality decayed within 30 min, while patients' perceived speech effort benefit lasted 60 min. There was no conclusive evidence for longer term benefit from VTS at the end of the trial. There was also no significant difference in the benefit between the 40 Hz versus the 100 Hz treatment groups, suggesting lower frequency stimulation is sufficient. The study raised questions about the potential benefits of stimulation, with possibility of repetition and duration adjustment for future studies.

The University of Minnesota further studied VTS usability at home, "Usability of Laryngeal Vibro-tactile Stimulation as a Non-invasive Treatment for the Voice Disorder Spasmodic Dysphonia." [114] This Phase 1/2 trial in 32 participants applied vibrators to both sides of the larynx with frequency set to 100 Hz. One cohort had a wearable collar with embedded vibrators while the other cohort manually taped the device to the skin. Participants were asked to use the device for increasing periods of time weekly for 4 weeks at the participant's discretion. The primary outcome measure was perceived vocal effort on a 0–10 scale, while secondary outcomes assessed the number and duration of voice breaks recorded remotely using smartphone applications. This study concluded in 2024. Preliminary results from the University of Minnesota website [115] reported equal effectiveness in the collar-delivered and direct skin vibration cohorts. Further details regarding degree of benefit or efficacious duration have not been published yet.

The University of Minnesota plans to continue studying VTS in laryngeal dystonia. The trial, "Laryngeal Vibro-tactile Stimulation as a Non-invasive Symptomatic Treatment for Spasmodic Dysphonia" began in January 2025 [116]. This study will investigate VTS efficacy as a neuromodulation treatment for both adductor and abductor laryngeal dystonia. This Phase 2 randomized crossover study will enroll 60 participants who will place the VTS device above the thyroid cartilage, delivering stimulation at 40–100 Hz. The study will test four experimental groups receiving low- or high-dose VTS, either continuously or during speech tasks, for 20 min per session, up to seven times per week. Primary outcomes include perceived speech effort, voice quality, and speech quality vector. This trial aims to gather data that may support VTS as a viable, non-invasive alternative to current laryngeal dystonia treatments, refining stimulation parameters and determining long-term effectiveness. The study started January 2025 and will complete in August 2026.

The University of Florida expanded VTS research beyond laryngeal dystonia, exploring its effects on essential tremor, PD and dystonia [117]. Their crossover study, which enrolled 40 participants, assessed whether skin-surface vibration could enhance motor function and reduce abnormal movements. Patients were instructed to withhold any neurologic medication for 12 h prior to testing. For the five patients with cervical dystonia, the device was applied to the skin of the neck. VTS discharged continuous, intermittent and sham stimulation during physical exam of symptomatic basic tasks of motor control [118]. The primary outcome measures were based on TWSTRS and Clinical Global Impressions scales before and after stimulation. This study seeks to demonstrate VTS's potential for

improving different movement disorders. This study was completed in September 2022; results have not yet been published.

Transcutaneous electric nerve stimulation (TENS)

Pain is a major disabling factor in cervical dystonia and is often the reason patients seek therapeutic relief. Transcutaneous electrical nerve stimulation (TENS) has demonstrated moderate-certainty evidence for efficacy and safety for acute and chronic pain conditions in a meta-analysis of 381 randomized clinical trials [119]. The Central Hospital in Nancy, France completed a TENS clinical trial in 2020: "Relief of Pain in Patients with Cervical Dystonia Through the Use of Sensory Threshold TENS." [120] This observational, prospective, single arm study enrolled patients who benefited from BoNT for painful cervical dystonia. Patients with pain persisting 2 weeks after a BoNT injection were given a demonstration of how to use TENS. They were able to continue to use TENS until follow-up at next injection cycle 12–16 weeks later. TENS was applied to posterior cervical muscles or close to the painful site. The duration of device usage throughout the day, except during sleeping and driving, was left to patient's discretion. The results were published in which median duration of TENS use was 72.3 min per day; total TWSTRS in 15 participants had an average of -8-point change from baseline (±4.62, 95% CI -1 to −9.13, p = 0.0001) [121]. These findings suggest TENS is a safe, therapeutic method for pain relief in cervical dystonia.

Neurofeedback brain-computer interface

Brain-computer interface (BCI) is a device being utilized in neurologic disorders other than dystonia to restore function. BCI uses analysis of an individual's brain signals to generate a command to an output device that can then carry out the impaired function. This is an evolving field in neurorehabilitation. Simonyan et al. [122] outlined a recommendation for a "noninvasive, closed-loop neurofeedback BCI intervention paradigm" in which a disordered EEG signature is detected during an action that elicits the individual's dystonic symptoms, and a target EEG signature is generated based on recordings during an asymptomatic task. During training, individuals would be asked to perform a symptomatic task while actively trying to modify their EEG activity until it matches the target EEG signature. Through this feedback loop, it is hypothesized that the patient may have symptom reduction over time. The Massachusetts Eye and Ear Infirmary is testing this paradigm through a Phase 1, randomized, sham-controlled clinical trial, "Adaptive Closed-loop Brain-computer Interface Therapeutic Intervention in Laryngeal Dystonia." [123] Patients undergo 5 days of treatment in which the target signature is identified as the EEG pattern during whispering and the disordered signature is generated during their spasmodic dysphonic speech. After 5 days, a perceptual voice analysis system will be used to measure the change in the number of dystonic voice breaks as the primary outcome. This study plans to enroll 40 patients and is actively recruiting.

Exercise, rehabilitation, and osteopathic manipulation

Dystonia requires a holistic, comprehensive approach to treatment. Not only limb dystonia can be debilitating, interfering with daily physical activity capabilities, but other forms of dystonia such as blepharospasm and cervical dystonia also impact physical capabilities due to proprioceptive and visual difficulties. Many patients with dystonia are referred for some form of rehabilitative therapy concurrent with pharmacological, medical, surgical or neuromodulatory management. Prudente et al. [124] published a systematic review of different rehabilitative interventions in dystonia in the prior 20 years. Unfortunately, the included studies presented with low or very low evidence quality and, as a result, the authors were unable to generate reliable recommendations for the rehabilitation approaches.

The University of Florida conducted a five-year study on, "Exercise Training in Dystonia and Other Involuntary Movement Disorders." [125] It was a randomized prospective, controlled study in which 11 patients either received progressive resistance training or a modified fitness protocol. Exercises were required to be performed twice a week for initial 6 months with a trainer; then participants will continue regimen on their own for 3 years. Patients were required to receive stable doses of regular BoNT injections or oral pharmacologic therapy throughout the study period. The primary outcome was TWSTRS and BFMDRS (every 6 months) through 24 months compared to baseline. Although results have not yet been posted, this team has initiated an additional study with overlapping methods, "Progressive Resistance Exercise and Dystonia Pathophysiology." [126] This latter study aims to enroll 56 patients with predominantly focal cervical dystonia, who are being randomized into a standard of care control group versus a standard of care plus progressive resistance exercise-focused cervical and shoulder training cohort. The primary outcome measures are a comparison of functional MRI signals and TMS motor cortex excitability and plasticity at baseline and 6 months. This study may expand current understanding of the pathophysiology of cervical dystonia and potentially guide rehabilitative treatment protocols in the future. The study is

projected to complete in December 2027 and is actively recruiting.

Another exercise study related to botulinum toxin therapy in cervical dystonia is "Evaluation of the Effect of Personalized Exercise Program on Clinical Findings and Quality of Life of Patients with Cervical Dystonia Who Received Botulinum Toxin Type A Injection" [127] at Ankara University. This study aims to evaluate the impact of a personalized exercise regimen on 34 patients with cervical dystonia following BoNT treatment as there are debates on the benefit of exercise in patients receiving BoNT. Participants will be divided into two groups: (1) An intervention group who undergo a tailored exercise program incorporating stretching, strengthening, breathing, and rhythmic coordination exercises and (2) A control group who perform breathing and rhythmic exercises only. The study seeks to determine whether the 12-week exercise program improves clinical outcomes and quality of life, focusing particularly on pain relief measured via the TWSTRS as the primary outcome measure. Secondary outcomes will evaluate the disability and severity subscales of the TWSTRS as well as CDQ-34. This study is recruiting and anticipates completion in May 2025.

Prior case series and small studies have noted benefits of osteopathic manipulative treatment (OMT) in dystonia, especially cervical and foot dystonia [128]. The New York Institute of Technology conducted a randomized trial, "Osteopathic Manual Treatment of Postural Abnormality, Pain, and Autonomic Control of Cardiac Function in People with Parkinson's Disease and Truncal Dystonia" [129] The study investigated whether OMT could improve posture and heart rate variability in individuals with truncal dystonia and PD. Ten participants underwent eight weekly OMT sessions. Primary outcome measures were obtained at 8 weeks assessing changes in posture and heart rate variability. This study completed in September 2021; no results have yet been published.

Behavioral exercises are also being explored. The University of Hospital Schleswig-Holstein plans on is investigating the efficacy of a 12-month video-supervised training program for patients with writer's cramp. The study, "Treatment Effect and Relevance on Daily Life of a Video-supervised Sensorimotor Training Program and Its Influence on the Pathophysiology in Writer's Cramp" [130] randomizes patients into two groups: behavioral motor training through a sensorimotor training program and behavioral mindfulness awareness training. The study's primary outcome is the Canadian Occupational Performance Measure, which assesses self-perceived writing performance and satisfaction in daily life at baseline, 4, 8, and 12 months. Secondary outcomes include kinematic writing analysis using a digitizing tablet to measure handwriting regularity, WCRS, fMRI with serial reaction time, qualitative interviews for training feedback, and ADDS. The study is expected to enroll 54 participants. Primary completion is anticipated in January 2026; they are actively recruiting participants.

Discussion

The management of dystonia is complex and multifaceted due to its heterogeneous phenomenology. Recent and current clinical trials have investigated a widespread variety of treatment strategies. Some of these trials may also help further elucidate the underlying pathophysiology of dystonia.

In this narrative review, we summarize recent advances in therapeutic developments for dystonia, including medical treatments, toxin injections, surgical interventions, gene-targeted therapies, and rehabilitation approaches. For medical therapy, as the underlying pathophysiology of dystonia implicates multiple pathways and neurotransmitters and overlaps with other movement disorders, medications for other movement disorders are being investigated as potential therapeutic agents for dystonia. Botulinum toxin therapy continues to gain traction as a high yield area for research. An important recent advance in the field of BoNT therapeutics is the development of toxins with a potentially longer therapeutic window, such as daxibotulinumtoxinA, as well as other formulations being studied in dystonia to establish their efficacy, comparability, and potential for cost reduction. The field of surgical interventions, including deep brain stimulation and brain lesioning, has also made exciting progress. New DBS brain targets and innovative programming techniques are being explored. Ongoing studies are exploring biomarker-driven programming DBS programming which could address a challenge related to the delayed clinical effects of stimulation in dystonia. Novel brain lesioning techniques are being tested as an alternative to DBS. TMS has shown potential in small dystonia cohorts, but variability in its technique, administration, potency and response remain a barrier. Other non-invasive techniques, such as transcranial ultrasound stimulation and transcranial electrical stimulation, are being investigated. Gene therapy for dystonia remains in preliminary phases of clinical research at this point, but the field is rapidly advancing. Rehabilitation will always be an area of interest due to its safety and ability to be used in combination with other dystonia treatments. Vibration therapy, OMT, behavioral exercises, and neurofeedback training are all being explored as rehabilitative techniques and the studies suggest benefit in patient's quality of life as adjunctive therapy to first-line treatments.

Despite significant progress in understanding the neurobiology of dystonia, the development of new therapies has lagged. The clinical trials described in this paper are laying the foundation for future, larger clinical trials. For successful future clinical trials, development of sensitive and objective clinical outcome measures will be a crucial prerequisite. In the past 5 years, technology has helped improve objective data collection and outcome measures such as computerized approaches to objectively measure blinking activity in blepharospasm, kinematic sensors for multi-axial neck angle measurements in cervical dystonia, computerized systems that can evaluate gait parameters and pressure point changes in lower limb dystonia, goniometers for objective angle measurements in focal limb dystonia,

and vocal fold movement quantification using videoendoscopy and cepstral peak prominence measurements of voice quality in laryngeal dystonia. Another critical area is the establishment of biomarkers for dystonia. A number of potential disease biomarkers have been explored including PET scan, CSF neurotransmitter metabolites, TMS cortical excitability recordings, local field potential recording from DBS or other brain activity recordings. For future clinical trials, development of sensitive and objective clinical outcome measures will be a crucial prerequisite. Successful therapy development should be based on a precise understanding of pathophysiology, validated by sensitive clinical outcome measures in well-designed clinical trials, and supported by correlating changes in biomarkers.

As our understanding of the pathobiology of different dystonia subtypes advances [131–133], more druggable targets may emerge in the coming years. In addition, TMS exploration offers further insight into this network disorder [84, 134, 135]. Although a review of the pathophysiological aspects of different forms of dystonia (generalized, isolated, or secondary) was beyond the scope of the current review, it is becoming increasingly evident that a biology-tailored approach is essential for therapeutic development [136, 137]. Some efforts are already underway with ongoing efforts to repurpose already approved medications or natural supplements for specific genetic types of dystonia. These have shown promising results in preclinical studies and are now moving toward clinical testing.

The clinical trials described in this paper are laying the foundation for future, larger clinical trials. Ultimately, in clinical practice, treatment requires a patient-centered approach, in which physicians should consider integrating a multifactorial treatment plan for complex, refractory dystonia cases. Recent advancements and ongoing clinical trials will continue to open new avenues for future treatment modalities.

Author contributions

AL: Project execution, manuscript writing and review, tables and figures compilation, citation compilation; AM: Manuscript writing, tables and figures compilation; MS: Manuscript writing, tables and figures compilation; BK: Manuscript writing and review, citations review; HC: Project conception, manuscript review, citations review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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