# Dystonias: Clinical Recognition and the Role of Additional Diagnostic Testing

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## Abstract

Dystonia is the third most common movement disorder, characterized by abnormal, frequently twisting postures related to co-contraction of agonist and antagonist muscles. Diagnosis is challenging. We provide a comprehensive appraisal of the epidemiology and an approach to the phenomenology and classification of dystonia, based on the clinical characteristics and underlying etiology of dystonia syndromes. We discuss the features of common idiopathic and genetic forms of dystonia, diagnostic challenges, and dystonia mimics. Appropriate workup is based on the age of symptom onset, rate of progression, whether dystonia is isolated or combined with another movement disorder or complex neurological and other organ system features. Based on these features, we discuss when imaging and genetic should be considered. We discuss the multidisciplinary treatment of dystonia, including rehabilitation and treatment principles according to the etiology, including when pathogenesis-direct treatment is available, oral pharmacological therapy, chemodenervation with botulinum toxin injections, deep brain stimulation and other surgical therapies, and future directions.

**Keywords**
- dystonia
- diagnosis
- multidisciplinary treatment

## What Is Dystonia?

Dystonia, the third most common movement disorder after essential tremor and Parkinson's disease (PD), is characterized by the co-contraction of agonist and antagonist muscles resulting in abnormal postures and uncontrolled movement.[1] The contractions may be sustained or intermittent. Intermittent contractions may occur spontaneously or in a task-dependent manner. Dystonia can affect any body region and thus has varied manifestations.

## When Does Dystonia Begin?

Dystonia can occur at any point in life. In children, dystonia typically begins in a hand or foot and may or may not be associated with a delay in intellectual or motor development. Adult-onset dystonia typically occurs in someone who has met all developmental milestones. A common presentation for a school-age child is that s/he had trouble holding a pencil and writing clearly. As the child begins to write, the shoulder may become elevated, the forearm cannot rest on the table, the wrist becomes flexed, and the fingers flex uncontrollably around the pencil. At such a young age, some children may simply switch their dominant hand and not come to medical attention, unless the dystonia worsens and/or affects additional body regions. Children have the greatest likelihood of developing spread of dystonia, with unilateral limb onset resulting in involvement of the contralateral side or spreading from an arm to one or both legs.

Adult-onset dystonia is more likely to affect the neck or craniofacial muscles, causing uncontrolled turning or tilting of the neck, uncontrolled eyelid spasms or jaw movements.

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However, adults can also develop task-specific focal dystonia, which when present in a hand/arm, can result in writer's cramp, or when playing a musical instrument, musician's dystonia, and when involving the lower extremities, involuntary leg/foot posturing when walking or running. Over time, these task-specific dystonias can lose their task-specificity and become present at rest. In most cases, adult-onset focal dystonia may progress and then plateau; however, some can be progressive.[2]

## Dystonia: Phenomenology and Epidemiology

Dystonia is a clinical diagnosis, based on the systematic observation of a patient. The primary physical sign is muscle contractions that may be continuous, intermittent, or task-specific, forcing a limb, trunk, or the neck into a sustained, abnormal posture with reduced range of motion. This is frequently accompanied by the patient describing a sensation of pulling or twisting of the involved body part toward a certain direction. A common complaint for individuals with cervical dystonia is that the neck tends to turn to one side, and it is difficult or takes conscious thought to turn fully to the opposite direction. Thus, individuals with cervical dystonia may first notice difficulty while driving or when trying to read a book. A common form of task-specific dystonia is writer's cramp. Individuals with writer's cramp may be able to button a shirt and type without difficulty, but are unable to grasp a pen and write, as the wrist begins to move uncontrollably, and the upper arm and shoulder may elevate. Similar dystonia can involve other common hand tasks, such as typing on a computer keyboard, on a mobile phone, or drawing/painting. Dystonia may be worsened with voluntary movement of the affected body part. For example, an individual with cervical dystonia with uncontrolled head turning to the right may experience stronger contractions when trying to move out of the abnormal position. Additional signs of dystonia include the following: (1) the presence of a sensory trick (*geste antagoniste*), a simple touching of the affected body region, or other simple movement that reduces the severity of the dystonic movement; (2) mirror dystonia in those with limb dystonia, which consists of dystonic movement in the unaffected, contralateral limb, when the affected limb is performing repetitive tasks such as finger or toe tapping or when writing with the contralateral hand; and (3) overflow dystonia, in which there is a dystonic contraction in an adjacent body region that is anatomically distinct from the affected region, and observed when the affected body part is displaying prominent dystonic activity. Dystonia may be associated with a dystonic tremor, which is typically jerky and irregular, with a positional quality, and worse with attempts to maintain a normal posture, rather than assuming the abnormal posture caused by the dystonia itself.[3,4] The dystonic movement is generally patterned, displaying a consistent and predictable pattern. For example, in individuals with cervical dystonia, there is typically a consistent pattern of head turning in one direction, with emergence of a dystonic tremor when the affected individual tries to straighten the head and particularly when moving to the direction opposite the pulling. There can also frequently be a "null point" where the dystonia or dystonic tremor is minimized. In addition, dystonia is typically worsened by anxiety, stress, or heightened emotion (whether positive or negative) and when tired or fatigued, which historically had led to concern that cases may be functional.[5] Dystonic movements generally resolve during sleep.[6]

Owing to the heterogeneous nature of dystonia, epidemiologic data are limited. A meta-analysis suggested an overall prevalence of isolated focal dystonia of 16.4 per 100,000 individuals.[7] Focal dystonia is more common than cases with a wider distribution (segmental, multifocal, and generalized). Cervical dystonia is the most prevalent isolated dystonia, at 3 to 13 per 100,000.[7] However, data from Japan and Italy suggest blepharospasm being more common than cervical dystonia.[8–11] While rare in childhood, dystonia is progressively more common with advancing age. Prevalence rates of early-onset dystonia, defined as onset before the age of 20, are 0.2 to 5 per 100,000, in comparison to 3 to 732 per 100,000 for late-onset dystonia, defined as onset at 20 years of age or older.[7] In a door-to-door study in India, dystonia prevalence in those less than 30 years of age was 7.7 per 100,000, whereas dystonia prevalence in those between 50 and 70 years of age was 177.9 per 100,000.[12]

## Dystonia Classification

Once the clinical features of dystonia have been identified with a high degree of certainty, the next question is how best to formulate a differential diagnosis and pursue possible causes. First, it is helpful to classify the dystonia based on history and examination features. In 2013, the classification algorithm for dystonia was revised and involves placing patients along two different axes: first, the clinical features of dystonia and, second, the presumed underlying etiology[13] (►**Table 1**). As per Albanese et al, Axis 1 (Clinical characteristics) includes factors indicating the dystonia subtype: age of onset, distribution of dystonia, temporal pattern of the dystonic movements, and whether there are any associated neurological or other clinical features.[13] In comparison, on assessing Axis 2 (Etiology), the clinician should indicate whether there is evidence for an underlying, identifiable nervous system pathology, and whether inherited, acquired, or idiopathic.[13] Changes in genetic dystonia nomenclature (from previous locus designations DYT1, DYT6, etc.) were updated in 2022 to reflect the predominant or combined movement phenotype associated with each confirmed monogenic movement disorder (e.g., DYT/PARK-TAF1 [previously DYT3]).[14]

### Axis 1: Clinical Characteristics of Dystonia

Age of onset can be subdivided into infantile (0–2 years), childhood (3–12 years), adolescent (13–20 years), early adult (21–40 years), and late adult onset (>40 years, the most common).[13] This is important, as there are different age distributions associated with different dystonia subtypes. Dystonia that begins below the age of 20 generally starts

 

**Table 1** Classification of dystonia

| **Axis I. Clinical characteristics** | |
|---|---|
| **First rule-out pseudodystonia**[a] | |
| Age of onset | • Infancy (birth to 2 y)—genetic/birth injury and other acquired<br>• Childhood (3–12 y)—genetic/acquired<br>• Adolescence (13–20 y)—genetic/acquired<br>• Early adulthood (21–40 y)—genetic/idiopathic/acquired<br>• Late adulthood (>40 y)—more likely idiopathic after age 50/acquired/genetic |
| Body distribution | • Focal (1 body part involved)<br>- Eyelids (blepharospasm)<br>- Oromandibular dystonia (including task-specific embouchure dystonia)<br>- Laryngeal dystonia/spasmodic dysphonia (including singer's dystonia)<br>- Cervical dystonia<br>- Hand/arm (including task-specific writer's cramp and musician's dystonia), foot/leg (including task-specific running dystonia), trunk (including camptocormia/Pisa syndrome)<br>• Segmental (≥2 contiguous body parts)<br>- Meige syndrome (eyes and lower face with or without neck involvement)<br>- Axial (neck and trunk)<br>- Brachial (arm and trunk; both arms with or without neck or trunk involvement)<br>- Crural (leg and trunk; both legs with or without trunk involvement)<br>• Multifocal (≥2 contiguous body parts)—faciobrachial (blepharospasm and writer's cramp)<br>• Hemidystonia (≥2 contiguous body parts, same side)<br>• Generalized (≥3 body parts)—trunk and ≥2 other sites; with or without leg involvement |
| Temporal pattern | • Disease course—static vs. progressive<br>• Variability<br>- Persistent—dystonia stays a same level throughout the day (most causes of dystonia)<br>- Action/task-specific—only occurring during specific task or action (e.g., writer's cramp, musician's dystonia, runner's dystonia, singer's dystonia, other occupational dystonias)<br>- Diurnal—dystonia fluctuates with circadian variation (e.g., dopa-responsive dystonia)<br>- Paroxysmal—sudden episodes of dystonia, typically induced by a trigger (e.g., paroxysmal kinesigenic dystonia, paroxysmal non-kinesigenic dystonia, paroxysmal exercise-induced exercise/exertion-induced dystonia—there is significant clinical/genetic overlap between these) |
| Associated features | • Isolated dystonia (dystonia only features)<br>• Combined dystonia (dystonia combined with another movement disorder, commonly parkinsonism, myoclonus, or ataxia)<br>• Complex dystonia (other neurological features, including cognitive/neuropsychiatric symptoms, weakness, spasticity, cranial nerve abnormalities, etc.) |
| **Axis II. Etiology** | |
| Nervous system pathology | • Brain degeneration (e.g., X-linked dystonia parkinsonism [XDP], neurodegeneration with brain iron accumulation disorders)<br>• Structural brain lesions (e.g., strokes, tumors, demyelination)<br>• No evidence of degeneration or structural lesion (majority) |
| Inherited dystonia | • Autosomal dominant (e.g., DYT-TOR1A, DYT-THAP1)<br>• Autosomal recessive (e.g., DYT-HPCA)<br>• X-linked recessive (e.g., X-linked dystonia parkinsonism/DYT/PARK-TAF1)<br>• Mitochondrial (e.g., Leber's hereditary optic neuropathy/DYT-mt-ND6) |
| Acquired dystonia | • Perinatal brain injury (e.g., post-cardiac arrest, "cerebral palsy," bronchopulmonary dysplasia, hypoglycemia)<br>• Infection (e.g., Creutzfeldt-Jakob disease, *Mycoplasma pneumoniae*, tuberculosis, Japanese B encephalitis)<br>• Parainfectious (e.g., Reye syndrome, subacute sclerosing panencephalitis)<br>• Autoimmune disorders (e.g., multiple sclerosis, antiphospholipid-antibody syndrome, autoimmune/paraneoplastic encephalitis)<br>• Metabolic disorders (e.g., kernicterus, hepatic encephalopathy, hypoparathyroidism, osmotic demyelination syndrome)<br>• Vascular (e.g., stroke sequelae of basal ganglia lesions, arteriovenous malformation of the basal ganglia)<br>• Traumatic brain injury<br>• Intraparenchymal space-occupying lesions (e.g., brain abscess, tumor, or other space-occupying lesion, including from radiation)<br>• Physical interactions (e.g., electrocution, ionizing radiation/radiation therapy) |

(*Continued*)

**Table 1** (*Continued*)

| | |
|---|---|
| | • Toxic (e.g., carbon monoxide, methanol, disulfiram, or cyanide poisoning, manganese, wasp sting encephalopathy)<br>• Drug-induced (e.g., acute dystonic reactions, tardive dystonia)<br>• Functional/Psychogenic—strictly a pseudodystonia which can mimic all forms of dystonia |
| Idiopathic | • Sporadic (most focal or segmental dystonias)<br>• Genetic (most multifocal, or generalized dystonias) |

Source: Adapted from Albanese et al.[13]

focally in a distal limb and is more likely to spread to other body regions. Dystonia that begins over the age of 20 is typically focal (most commonly affecting the neck, eyes, or less commonly a limb) or segmental (commonly craniocervical in distribution).[15] In addition, late-onset dystonia (>40 years) tends to begin earlier in the upper extremity and neck (cervical), as opposed to the face, jaw, and/or tongue (cranial).[16] Cervical dystonia has a typical age of onset in the fourth and fifth decades (mean age: 41.7 years),[17–19] whereas spasmodic dysphonia (laryngeal dystonia) tends to occur slightly later (mean age of onset: 50.1 years).[17] In contrast, cranial dystonia, composed of blepharospasm or oromandibular dystonia or a combination of both (Meige syndrome) occurs later, generally in the sixth and seventh decades.[20] Late-onset focal limb dystonia occurs earlier, in the fourth decade.[20]

Body distribution is defined based on the body region affected: (1) focal, if only a single body region is affected; (2) segmental, if two or more adjacent body segments are affected; (3) multifocal, if at least two noncontiguous body regions (such as hand and foot) are affected; and (4) generalized, if the trunk and at least two other sites are affected. Hemi-dystonia, where there is unilateral combined upper and lower extremity involvement, is considered separately, and often related to acquired dystonia from a contralateral brain lesion.[2,21]

The temporal pattern is subdivided into four distinct categories: (1) persistent, (2) action-specific/task-specific, (3) diurnal fluctuation, and (4) paroxysmal. In a persistent pattern, the dystonia is generally stable throughout the day (although can be exacerbated by stress or other aggravating features). An action- or task-specific dystonia is a form of dystonia occurring only when a specific activity is performed. In the upper extremities, this typically involves a fine motor activity requiring precision, such as writing, typing, or playing a musical instrument. In the lower extremities, precision tasks can be involved (such as dance/ballet), while endurance tasks such as running or cycling are more common. Task-specific dystonia can involve other tasks, or even occur at rest over time.[22] A diurnal fluctuation in dystonia severity may be found, particularly in childhood-onset dopa-responsive dystonia.[23] However, many individuals find that the dystonia worsens somewhat as the day progresses, presumably associated with increased general fatigue. Lastly, paroxysmal dystonia occurs in sudden, discrete episodes, often associated with specific triggers (movement, exercise, eating certain foods, physical/emotional stress), followed by a return to the neurological baseline.[24–26] Paroxysmal dystonias very rarely occur after the age of 18, unless there is an underlying lesion in the central nervous system. Occasionally, the dystonic movements may co-occur with other hyperkinetic phenomena, such as chorea or myoclonus; hence, the term paroxysmal "dyskinesia" is also used. The persistence of the hyperkinetic movements after cessation of the trigger distinguishes paroxysmal dystonia from other forms of dystonia. In contrast, in task- or action-specific dystonia, the dystonia is present only when performing the inducing task.[13]

The presence or absence of non-dystonic clinical features is important to identify, because if non-dystonic neurological features are present, this indicates a far less common scenario and helps in honing the differential diagnosis. Dystonia can either be the only abnormal movement phenotype present (aside from associated tremor), indicating an *isolated* dystonia, or may be *combined* with another movement disorder. In *combined* dystonia, there is the presence of another movement disorders in addition to dystonia, most frequently parkinsonism, myoclonus, or ataxia.[27–29]

## Axis 2: Etiology of Dystonia

The etiology of dystonia is an area of rapidly evolving research. However, identifying possible etiologies for a particular form of dystonia can help the treating clinician determine the extent of the workup required and help with selecting treatment. A history of intellectual or motor delay in childhood-onset dystonia helps direct the extent of imaging and genetic testing that may be helpful. Signs of additional movement disorders, cognitive dysfunction, or other complex neurologic features in early or late adult-onset dystonia also help direct the clinician in selecting additional testing.

### Adult-Onset Idiopathic Focal/Segmental Isolated Dystonia

Adult-onset idiopathic focal and, less often, segmental dystonias are the most common forms of dystonia overall and are not associated with features indicating a specific cause.[2] These tend to be persistent and less frequently task-specific. Rarely, spontaneous remission occurs within the first 5 years after onset. However, the majority subsequently relapse.[28]

The most common adult-onset focal/segmental dystonia affects the cervical region. This often begins in middle age (30s–50s), frequently initially with neck pain, followed by the development of an abnormal neck posture or jerky head tremor. The form of abnormal posturing can involve neck turning or rotation, flexion, extension, lateral flexion, or a combination of these postures. In some cases, a dystonic

 

head or hand tremor is seen, which may mimic essential tremor.[4] Sensory tricks, involving gentle touching of the head or neck, are frequently beneficial,[30] although this may wane over time.[28] As described earlier, pain is a frequent and early feature, related to sustained abnormal postures caused by asymmetric muscle contraction, or the rapid alternating activation of agonist/antagonist muscles in dystonic tremor, leading to focal muscle spasm in these overused muscles and is associated with a reduced quality of life.[31,32] Patients may report a family history of dystonia and tremor in up to 14% and 29% of cases, respectively, which is suggestive of polygenic inheritance akin to essential tremor.[33]

Cranial dystonia involves abnormal contractions of the muscles of the face and head. Subtypes include involvement of the eyelids (blepharospasm), lower face (rarely isolated and generally combined with eyelid spasms in Meige syndrome, or hemifacial spasm), or the jaw or tongue (oromandibular dystonia), either in isolation or in combination. Local spread within the cranial region tends to occur generally over months or years after initial onset, as well as extracranial spread to the neck and upper extremities with older age.[34,35] Blepharospasm is the most common form. Initially, affected individuals present with mild symptoms of increased bilateral eyelid blinking, sometimes triggered by bright light exposure.[36] If left untreated, the blinking increases in frequency and may evolve into more prolonged spasms, which can be sight-limiting, and approximately 12 to 36% can become functionally blind.[6] Concurrent lower facial spasms indicate segmental craniocervical dystonia, called Meige syndrome. Sensory tricks include lightly touching the eyelids, applying pressure over the superior orbital ridges or canthus, or rubbing the eyes.[35]

Oromandibular dystonia includes dystonic involvement of various jaw and mouth muscles. This can present with involuntary jaw opening, closing, lateral deviation, protrusion, or retraction movements, with or without jaw tremor. Like cervical dystonia, the uncontrolled muscular contraction frequently leads to muscular overuse, resulting in jaw tension, pain, and spasms, and may also present as bruxism.[37] Activation of these muscles through talking and chewing typically results in symptomatic worsening[38]; however, there are rare cases with paradoxical improvement when talking or with certain tongue positions.[39] Sensory tricks can include pressure on the lips or teeth, touching the tongue to the hard palate, chewing gum, or placing an item such as a tongue depressor or toothpick between the teeth or in the cheek.[6] Oral prosthetics have been used with some success.[40] Tongue dystonia is a rare oromandibular dystonia and involves tongue protrusion or curling and can also cause drooling.[41] Lingual dystonia most commonly occurs with speaking, and can cause problems with speech, eating, and swallowing.[42]

Laryngeal dystonia (or spasmodic dysphonia) affects the vocal folds, causing speech or singing difficulties. It is subdivided into two main forms, involving either adductor muscles (presenting with strained, strangled, and coarse speech) or the abductor muscles (causing breathy speech, worse with voiceless consonants). Spasmodic dysphonia is more common in women, and the adductor type is more frequent. An associated dystonic voice tremor is encountered in up to 30% of cases.[43,44] A useful clinical clue is that innate vocalizations (e.g., during laughing, crying, or whispering) tend not to be affected. Vocal difficulties may worsen with stress, when talking on the telephone or when attempting to project the voice, such as when speaking in public.[43]

Limb dystonias are infrequent in adult-onset cases and are often task-specific.[12,13] The most common upper limb dystonia is writer's cramp, a task-specific dystonia affecting the hand, forearm, or upper arm with writing.[25] Writer's cramp is more common in males, generally occurs in middle age, particularly the fourth decade, and may lose its task-specificity and involve other hand tasks or even spread to the contralateral hand over time.[23] Musician's focal hand dystonia generally involves contraction of the fingers (frequently finger flexion) or wrist (less frequent) when playing a musical instrument. Musicians may also develop embouchure dystonia, a task-specific oromandibular dystonia, affecting the way the mouth or tongue is applied to a woodwind or brass instrument.[45] Like writer's cramp, musician's dystonia is more common in males, and professional musicians, with onset often during the peak of their performance careers. Precipitants include excessive practicing or other hand injury,[46] as well as peripheral nerve entrapment in the motor distribution of the affected fingers, particularly ulnar nerve entrapment, with the most common pattern being dystonic flexion of the ring and little fingers.[47] Task-specific lower extremity dystonia often involves running but can also affect other tasks, such as cycling or walking on certain terrain.[11] Abnormal posturing predominantly involves plantar flexion but may also involve proximal or distal muscles.[12] Adult-onset lower limb dystonia when isolated (e.g., not in the setting of PD) often begins with a specific lower extremity action, but frequently progresses to affect routine walking.[12] In addition, task-specific dystonia has also been reported in several different sports.[47]

## Workup

►**Table 2** depicts a recommended evaluation, based on the distribution of dystonia, age of onset, presence of developmental delay, or signs of parkinsonism, ataxia, or other movement abnormalities in adults, and the presence or absence of a family history of movement disorders. For those developing dystonia before the age of 30 years, an evaluation including copper studies (ceruloplasmin and 24-hour urinary copper) to rule out Wilson's disease and magnetic resonance imaging (MRI) of the brain followed by genetic testing is recommended. A diagnostic testing algorithm for dystonia is detailed in a recent review.[27] Next-generation–based sequencing, ideally of all coding regions (exome sequencing) or when available, including non-coding regions (genome sequencing, which encompasses intronic regions), is the state of the art for determining genetic causes. Often, investigation may be initiated with a specific gene panel, targeting the analysis to a subset of genes involved with dystonia. This approach may be more cost-conscious; however, there is great laboratory heterogeneity when selecting the included genes and the frequency with which these

 

**Table 2** Evaluation and workup of dystonia

| Clinical characteristics | | | | Main diagnostic considerations | Workup | | | |
|---|---|---|---|---|---|---|---|---|
| **Dystonia distribution** | **Age at onset** | **Developmental delay, parkinsonism or other movement disorder** | **Family history** | | **Laboratory testing[a]** | **MRI** | **Genetic testing[b]** | **Levodopa trial** |
| Focal | < 30 y | Y | Y or N | Genetic; acquired (nonprogressive, no FH) | Y | Y | Y | Y |
| Focal | < 30 y | N | Y or N | Genetic | Y | Y | Y | Y |
| Focal/Segmental | < 30 y | Y or N | Y or N | Genetic; acquired (nonprogressive, no FH) | Y | Y | Y | Y |
| Focal/Segmental | ≥ 30 y | N | N | Idiopathic | N, unless atypical features | N | N | Y or N (consider if features of DRD) |
| Focal/Segmental | ≥ 30 y | Y | Y or N | Genetic; Acquired (nonprogressive, no FH) | Y | Y | Y | Y |
| Generalized | Any | Y or N | Y or N | Genetic; acquired (nonprogressive, no FH) | Y | Y | Y | Y |
| Hemidystonia | < 30 y | Y or N | Y or N | Acquired; genetic (particularly DRD) | Y, if MRI negative | Y | Y, if MRI negative | Y |
| Hemidystonia | ≥ 30 y | N | Y or N | Acquired > genetic | Y, if MRI negative | Y | Y, if MRI negative | Y, if MRI negative |
| Paroxysmal | < 20 y | Y or N | Y or N | Genetic | Y ± CSF (exercise-induced) | Y | Y | N |
| Paroxysmal | > 20 y | N | N | Functional > genetic | Y or N | Y or N | Y or N | N |

Abbreviations: CSF, cerebrospinal fluid; DRD, dopa-responsive dystonia; FH, family history; N, no; Y, yes; y, years.
Notes: In all cases, pseudodystonia should be ruled out.[6] If there is temporal association with treatment with a dopamine receptor blocking medication (antipsychotic, metoclopramide, etc.), then initial concern should be for a tardive dystonia. Note that functional dystonia may mimic any form of dystonia but has specific "rule-in" historical and examination features.[5]
[a]Recommended laboratory testing workup: adults and children—copper, ceruloplasmin, 24-hour urinary copper, coenzyme Q10 level; children—serum amino acids, urine organic acids, other testing as indicated.
[b]Recommended genetic testing: Single gene testing if other family members with known genetic dystonia (or if high index of suspicion given other features, such as ancestry and clinical features highly suggestive of a single genetic dystonia); if not, dystonia gene panel and following this, clinical exome/genome sequencing.

panels are updated to reflect novel findings. Therefore, a negative panel should be interpreted with caution based on knowledge of the genes comprised and their pre-test probability. The choice of which gene panel to order is based on a combination of the presence or absence of either developmental delay, or features of parkinsonism or other movement disorder on exam. The presence of a positive family history or parental consanguinity may be a clue when ordering genetic tests. However, even in the absence of such history, one should consider genetic testing when investigating individuals with onset younger than 30 years. This is the case for several reasons. First, a particular inheritance pattern may not be obvious in individuals with limited family history. Second, some genetic dystonias have variable penetrance. Lastly, several recently identified gene mutations in diseases with autosomal dominant inheritance have been identified "de novo."

For those individuals who develop isolated focal or segmental dystonia over the age of 30, the family history is informative in determining next steps. When there is a first-degree relative with dystonia or parental consanguinity, a brain MRI and genetic testing should be considered. For those individuals with onset with isolated focal or segmental dystonia without a family history, no further workup is necessary and the patient can be treated symptomatically. However, these patients should be monitored over time for the rate of progression, spread of dystonia, or development of other features that may indicate the need for genetic testing.

 

## Genetic Testing in Dystonia

Genetic testing should be performed only if there is explicit and informed consent from the patient and, if possible, pretesting discussion of the possible outcomes and implications with a genetic counselor. This is particularly important when broad testing strategies are applied, such as when ordering exome sequencing which may disclose incidental findings. Identifying the genetic cause of a dystonia can help guide treatment options, such as the use of levodopa in dopa-responsive dystonia, copper chelating agents in Wilson's disease, and low-dose antiseizure drugs in paroxysmal kinesigenic dyskinesia. Individuals with certain genetic dystonias, including DYT-TOR1A, DYT-SGCE, and DYT-KMT2B, tend to respond more favorably to treatment with deep brain stimulation (DBS), whereas DYT-ATP1A3 dystonia does not.[48] The number of gene mutations that results in dystonia grows annually. ►**Table 3** shows the key features of both common and rare genetic forms of dystonia. Here, we briefly discuss those gene mutations for which evidence indicates a specific treatment path.

### Autosomal Dominant Isolated Dystonia

DYT-TOR1A (DYT1) dystonia, is caused by an in-frame heterozygous deletion of a glutamic acid residue in *TOR1A*. This is the most common cause of early-onset generalized dystonia, particularly in individuals of Ashkenazi Jewish ancestry, where this accounts for 80 to 90% of early-onset dystonia (16–53% in other populations),[49] with a gene prevalence of 1 in 3,000 to 1 in 9,000.[26] DYT-TOR1A typically begins focally in a distal limb during childhood or adolescence but frequently generalizes over months to years in up to half of patients.

DYT-THAP1 (DYT6) dystonia is caused by heterozygous variants in the THAP1 gene, a transcription factor, with reduced penetrance.[50] Recent evidence indicates that DYT-THAP1 mutations result in dysregulation of genes associated with neurodevelopment, lysosomal lipid metabolism, and myelin.[51] DYT-THAP1 frequently presents as a craniocervical dystonia or in an arm, and less frequently involving the oromandibular region, and may become generalized.[50,52] *THAP1* mutations have been identified in both familial and sporadic cases and there is reduced penetrance.[53,54]

Recently, vacuole protein sorting (VPS) gene *VPS16* has been demonstrated as a rare cause of autosomal dominant early-onset isolated dystonia, DYT-VPS16, which progressively generalizes and has reduced penetrance.[55] DYT-VPS16 has been associated with jerky myoclonus, occasional intellectual disability, neuropsychiatric symptoms, and subtle signs of brain iron accumulation.[55] DBS was found to be significantly beneficial in some cases and some cases were levodopa-responsive.[55–57]

### Autosomal Recessive Isolated Dystonia

Autosomal recessive dystonia is much less common than its autosomal dominant counterparts but can be suspected if there are multiple affected individuals within the same generation, or if there is parental consanguinity. Compound heterozygous mutations in the *HPCA* gene (which encodes a neuronal calcium sensor protein) are uncommon and have been identified in a single kindred of early-onset dystonia, which tended to begin craniocervically and slowly generalize.[58] While DYT-VPS16 appears to have mainly autosomal dominant inheritance, there have been cases of homozygous mutations.[59] Another VPS gene, *VPS41* has been associated with biallelic variants causing global developmental delay and generalized dystonia.[55] There are reports of homozygous variants in DYT-THAP1 and DYT-GNAL, suggesting that these mainly dominantly inherited genes may also present in a recessive manner.[52,60] There is an uncertain role for COL6A3.[61]

### Combined Genetic Dystonia

Combined dystonias include other movement disorders, such as parkinsonism, myoclonus, or ataxia.[29] Cases of dystonia-parkinsonism can include mutations in the *TAF1*, *GCH1*, *ATP1A3*, *PRKRA*, and *VAC14* genes, as well as a complex dopa-responsive dystonia-parkinsonism syndrome related to genes encoding enzymes in the dopamine biosynthetic pathway, such as genes for tyrosine hydroxylase (*TH*) and sepiapterin reductase (*SPR*) genes.[62]

DYT/PARK-GCH1 (DYT5a) is an autosomal dominant dystonia with variable penetrance, caused by heterozygous GCH1 mutations (encoding guanosine triphosphate cyclohydrolase 1, critical for dopamine biosynthesis), resulting in a childhood-onset levodopa-responsive dystonia.[63] There is variable penetrance, reported to be higher in female individuals.[64] DYT5a dystonia typically begins as a focal foot dystonia, slowly spreads rostrally, and may generalize by adolescence.[63] There is a characteristic diurnal variation (milder morning symptoms, considerably worsening by the evening), which improves with a mid-day nap. A ubiquitous finding is the excellent response to low-dose levodopa therapy (typically $<$300 mg/day).

DYT-PRKRA (DYT16) is an autosomal recessive dystonia caused by biallelic pathogenic mutations in the *PRKRA* gene and was first identified in consanguineous families in Brazil.[65] Patients have early-onset limb or cervical dystonia, which may progress to severe generalized dystonia, including opisthotonos, sardonic facies, and laryngeal involvement, frequently associated with mild levodopa-nonresponsive parkinsonism.[65,66] More recently, *VAC14*-related dystonia-parkinsonism presents with childhood-onset generalized dystonia, may have brain iron accumulation on imaging, and may respond to DBS.[67]

DYT/PARK-TAF1 (DYT3) dystonia, X-linked dystonia parkinsonism (XDP), is caused by insertion of a retrotransposon SINE–VNTR–Alu (SVA) in TAF1 on the X chromosome.[68] A retrotransposon is a sequence of DNA, typically containing repetitive sequences, which is first transcribed into RNA and then converted back into DNA via reverse transcriptase and inserts into a different region of the genome. XDP is adult-onset (typically in the third to fifth decades), in males of Filipino ancestry (particularly Panay Island). This presents with focal dystonia, often involving the neck and jaw and generalizes, with varying degrees of parkinsonism, which

 

**Table 3** Genetic forms of dystonia

| Classification | Designation (gene locus) | Onset | Pattern of inheritance | Dystonia distribution | Other relevant features |
|---|---|---|---|---|---|
| Isolated dystonia | DYT-*TOR1A* (*DYT1*) | C | AD | Generalized | • **Most common genetic dystonia**<br>• Ashkenazi Jewish ancestry<br>• Reduced penetrance<br>• Frequently focal lower limb onset<br>• Cranial involvement rare<br>• **DBS highly effective** |
| | DYT-*THAP1* (*DYT6*) | A/C | AD (rarely AR) | Neck, limbs, orofacial, and larynx | • Prominent cranial involvement<br>• Reduced penetrance<br>• Focal arm onset<br>• **DBS beneficial** |
| | DYT-*ANO3* (*DYT24*) | A/C | AD | Neck, larynx, orofacial, and upper limbs | • Cervical/laryngeal onset<br>• Tremor, mimicking essential tremor |
| | DYT-GNAL (DYT25) | A | AD (rarely AR) | Neck, limbs, orofacial, and larynx | • Typical cervical onset<br>• Generalizes in childhood onset; often becomes segmental in adolescent onset |
| | DYT-*HPCA* (*DYT2*) | C | AR | Distal limbs, craniocervical, generalized | • Distal limb onset then craniocervical |
| | DYT-VPS16 | C/A | AR | Limbs, bulbar, cervical, generalized | • Reduced penetrance<br>• Focal onset, progressively generalizes<br>• Jerky myoclonus<br>• May have isolated dystonia<br>• Mild to moderate intellectual disability<br>• Neuropsychiatric symptoms<br>• **Subtle brain iron accumulation**<br>• Some levodopa-responsive<br>• **DBS potentially beneficial** |
| **Combined dystonia** Parkinsonism | DYT/*PARK-TAF1* (*DYT3*) | A | X-linked recessive | Orofacial, neck, limbs, and trunk | • **Filipino ancestry**<br>• Wide phenotypic spectrum from pure parkinsonism to pure dystonia; mainly dystonia parkinsonism<br>• Unique dystonic parkinsonian gait<br>• **DBS beneficial** |
| | DYT/*PARK-GCH1* (*DYT5a*) | C | AD (rarely AR) | Limbs and trunk | • **Levodopa responsive**<br>• **Diurnal variation**<br>• Spasticity |
| | DYT/*PARK-TH* (*DYT5b*) | C | AR | Limbs, trunk, and orofacial | • **Levodopa responsive**<br>• **Diurnal variation**<br>• Myoclonus<br>• Spasticity<br>• May have oculogyric crises<br>• **DBS beneficial** |
| | DYT/*PARK-SPR* | C | AR (rarely AD) | Variable | • **Levodopa responsive**<br>• **Diurnal variation**<br>• Intellectual/developmental delay<br>• High CSF biopterin/ dihydrobiopterin<br>• May have oculogyric crises |
| | DYT/PARK-*ATP1A3* (*DYT12*) | A/C | AD | Orofacial, cervical, larynx, and limbs | • **Clinical heterogeneity**: alternating hemiplegia of childhood; rapid-onset dystonia parkinsonism; CAPOS syndrome |

 

**Table 3** (*Continued*)

| Classification | Designation (gene locus) | Onset | Pattern of inheritance | Dystonia distribution | Other relevant features |
|---|---|---|---|---|---|
| | | | | | • **Rapid onset** after infection/febrile illness<br>• **Common subacute/rapid bulbar involvement**<br>• Exacerbations with fever, physical stress, alcohol<br>• May have seizures |
| | DYT-*PRKRA* (*DYT16*) | C | AD | Orofacial, larynx, neck, trunk, and limbs | • Limb/cervical onset<br>• Levodopa not beneficial<br>• **DBS potentially beneficial** |
| | DYT-*VAC14* | C | AR | Generalized | • Clinical heterogeneity: dystonia parkinsonism, developmental delay and retinitis pigmentosa, Yunis-Varón–like syndrome<br>• No documented levodopa responsiveness<br>• **Brain iron accumulation**<br>• **DBS potentially beneficial** |
| Myoclonus | DYT-*SGCE* (*DYT11*) | C | AD | Neck, upper limbs, and orofacial | • Often **mild dystonia**, with prominent myoclonus<br>• Alcohol dependence (improves myoclonus)<br>• **Neuropsychiatric symptoms**<br>• **DBS beneficial** |
| | DYT-*KCTD17* (*DYT26*) | A/C | AD | Cranial and cervical | • Scarce response to alcohol<br>• Initial mild upper extremity myoclonus/jerky tremor<br>• Later upper limb/craniocervical dystonia<br>• **DBS beneficial** |
| | DYT-*KMT2B* (*DYT28*) | C | AD | **Frequently generalized**, orofacial, larynx, neck, limbs, and trunk | • **Increasingly common cause of early-onset generalized dystonia** (may have isolated dystonia)<br>• Chorea and myoclonus<br>• Microcephaly<br>• Short stature<br>• Neuropsychiatric symptoms<br>• Intellectual/developmental delay<br>• Oculomotor apraxia<br>• **DBS beneficial** |
| Paroxysmal | PxMD-*PRRT2* (*DYT10*/*DYT19*) | C | AD | Variable | • Paroxysmal kinesigenic dyskinesia<br>• Attacks triggered by sudden voluntary movements, stress, startle, sleep deprivation<br>• Migraine (may be hemiplegic)<br>• ± Epilepsy<br>• Possible role for DBS |
| | TMEM151A | C | AD | Variable | • Paroxysmal kinesigenic dyskinesia<br>• Most without a family history<br>• Attacks very brief, predominantly dystonic<br>• ± Epilepsy |
| | PxMD-*PNKD* (*DYT8*/*DYT20*) | C | AD | Variable | • Paroxysmal nonkinesigenic dyskinesia with choreoathetosis, ballismus |

(*Continued*)

**Table 3** (*Continued*)

| Classification | Designation (gene locus) | Onset | Pattern of inheritance | Dystonia distribution | Other relevant features |
|---|---|---|---|---|---|
| | | | | | • Attacks triggered by alcohol, caffeine stress, hunger, fatigue, tobacco<br>• Possible role for DBS |
| | PxMD-*SLC2A1* (*DYT9*/*DYT18*) | C | AD | Legs most commonly | • Paroxysmal exertional dyskinesia with choreoathetosis |
| | PxMD-*ECHS1* | C | AR | Variable | • Paroxysmal exertional dyskinesia<br>• Severe developmental delay<br>• Infantile encephalopathy with choreoathetosis<br>• Optic atrophy<br>• Cardiomyopathy |
| | Autosomal dominant frontal lobe epilepsy (*CHRNA4*) | C | AD | Variable | • Paroxysmal hypnogenic dyskinesia |
| Other | DYT-*TUBB4A* (*DYT4*) | A/C | AD | Orofacial, larynx, neck, limbs | • **Whispering dysphonia**<br>• **"Hobby horse" gait**<br>• Ptosis, edentulous, facial atrophy<br>• ± Hypomyelinating leukodystrophy |
| | DYT-*MECR* (*DYT29*) | C | AR | Generalized | • Optic atrophy<br>• Basal ganglia abnormalities |
| | CHOR/DYT-*ADCY5* | C | AD, de novo, rare AD | Generalized | • Axial hypotonia<br>• Developmental delay<br>• **Facial twitching**<br>• Chorea<br>• Myoclonus<br>• Oculomotor apraxia<br>• Triggers: sleep transitions, emotional stress, illness, sneezing<br>• **Dyskinesias worse with sleep**<br>• Caffeine may be beneficial |
| | DYT-*ACTB* | C | AD | Generalized | • Sensorineural deafness<br>• Intellectual/developmental delay<br>• Dysmorphic facies<br>• **DBS beneficial** |

Abbreviations: A, adult onset; AD, autosomal dominant; AR, autosomal recessive; C, childhood onset; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss; CSF, cerebrospinal fluid; DBS, deep brain stimulation; XR, X-linked recessive.
Note: Bolding is used to emphasize important or pathognomonic features.
Source: Adapted from Frucht et al.[5]

tends to become prominent later in the course,[69] and may have a characteristic gait.[70] XDP can also present with isolated parkinsonism, indistinguishable from PD, which may have a more benign course.[69] XDP predominantly affects males, but females with skewed X-inactivation presenting with parkinsonism, and less frequently the full dystonia parkinsonism phenotype have been described.[71]

DYT/PARK-ATP1A3 (DYT12), also known as rapid-onset dystonia parkinsonism (RDP), is an autosomal dominant dystonia, caused by heterozygous *ATP1A3* mutations, with reduced penetrance. Presentation is typically in adolescence or early adulthood and is characterized by its acute or subacute onset of dystonia, often with prominent, early bulbar dysfunction, which may follow a triggering event, including physical (childbirth, excessive exercise, a fall, etc.), or psychological stress, or fever.[72] The dystonia can be associated with parkinsonism, particularly bradykinesia and postural instability.[73] Notably, the phenotypic spectrum of pathogenic variants in the *ATP1A3* has expanded rapidly in recent years, including other conditions such as alternating hemiplegia of childhood, CAPOS syndrome (*c*erebellar *a*taxia, *p*eripheral neuropathy, *o*ptic atrophy, and *s*ensorineural hearing loss) and developmental and episodic encephalopathy. Occasionally, some clinical features from these distinct syndromes may overlap.

DYT-KMT2B dystonia is autosomal dominant, with reduced penetrance, caused by mutations in the lysine-specific histone methyltransferase 2B gene (KMT2B), and is being increasingly recognized as a common cause of early-onset generalized dystonia (second only to DYT-TOR1A),[74] which

 

may be isolated but is frequently a combined dystonia.[75,76] There is a wide phenotypic spectrum, with complex features, such as developmental delay, microcephaly, or short stature, and other movement disorders including choreoathetosis or myoclonus.[75,76] Fortunately, akin to DYT-TOR1A, there is a good and sustained response to DBS.[77]

Lastly, DYT-SGCE dystonia is caused by mutations in the epsilon-sarcoglycan gene, with autosomal dominant inheritance. Individuals typically develop generalized myoclonus in early childhood, although mainly involving the head and arms but although classified as a dystonia, this part of the phenotype is often mild, generally involving cervical dystonia or writer's cramp.[78] Characteristic features include the considerable alcohol-responsiveness of the myoclonus (patients should be counseled regarding the risk of alcohol dependency for this reason), and prominent psychiatric features, including anxiety, depression, and obsessive-compulsive behavior.[79,80]

## Paroxysmal Dyskinesia/Dystonia

Paroxysmal dyskinesia/dystonia are rare childhood/adolescent-onset disorders involving discrete episodes of hyperkinetic movements, including chorea, dystonia, or myoclonus.[24,81] These rarely begin after 18 years of age. Thus, a clinical diagnosis of paroxysmal dyskinesia should be made with caution in those with symptom onset after 18 unless unequivocal suggestive symptoms and clinical signs, or a typical family history are present.

There are three main categories, although there can be significant overlap: (1) paroxysmal kinesigenic dystonia/ dyskinesia (PKD), (2) paroxysmal non-kinesigenic dystonia/ dyskinesia (PNKD), and (3) paroxysmal exercise/exertion-induced dystonia/dyskinesia (PED).

In PKD (most commonly caused by monoallelic mutations in the *PRRT2* gene, PxMD-PRRT2), characteristic features are that the episodes of dystonic or choreiform movements are brief (<1 minute), frequent (up to hundreds of times per day), and are triggered by sudden movement.[24,25] There is autosomal dominant inheritance with decreased penetrance. Individuals may also have a premonitory sensation such as paresthesia, fatigue, or sensation of muscle heaviness. *PRRT2* mutations can also cause benign infantile epilepsy, although seizures may be associated with fevers and tend to resolve by the age of 2 years.[16] Rarely, individuals with *PRRT2* pathogenic variants may present with episodic ataxia and/or hemiplegic migraines. Treatment of PKD is with antiseizure medication, frequently low-dose carbamazepine, as well as avoiding triggers.[24]

In PED (most commonly DYT-SLC2A1), onset is typically in childhood and episodes characteristically occur after prolonged exercise, have a variable frequency (ranging from several per day to one per month), and an intermediate episode duration (5–40 minutes).[24] The *SLC2A1* gene encodes the GLUT1 transporter, which is expressed on the blood–brain barrier and facilitates glucose delivery to the central nervous system. Patients with pathogenic variants in *SLC2A1* may present with varied paroxysmal symptoms in the context of GLUT1-deficiency syndrome, a condition with autosomal dominant inheritance but with frequent "de novo" mutations. A typical presentation involves foot dystonia (frequently foot inversion) after prolonged walking.[27] Triggers include fasting, stress, and anxiety.[24] Diagnosis is confirmed by a decrease in cerebrospinal fluid (CSF) glucose. CSF analysis is very useful for the diagnosis, since PED is genetically heterogeneous and occasionally next-generation sequencing technology may not pick up copy number variants that account for a small proportion of Glut-1 deficiency cases.[82,83] Management includes adhering to a ketogenic diet, and medical treatment with L-carnitine supplementation, or triheptanoin.[84]

PNKD (commonly monoallelic variants in PNKD gene, formerly MR-1), is autosomal dominant, with high penetrance, and episodes frequently have specific triggers, including physical conditions (exertion, ill health/fever, menstruation, psychological stress) or dietary triggers (methylglyoxal-containing foods such as alcohol, coffee, tea, or chocolate).[24] Characteristics of episodes include a variable but typically long duration (1 minute to 2 hours, up to 12 hours) and the absence of a motor trigger.[85] There tends to be a more dystonic appearance, which becomes more choreiform over time.[24] Patients may have a premonitory sensation prior to an episode, and patients note a benefit of sleep in 72.8%.[24] The mainstay of treatment is trigger avoidance, with some efficacy of oral medications, particularly benzodiazepines (clonazepam or diazepam), antiseizure medications (gabapentin or levetiracetam), and some reports of benefit from acetazolamide; however, the response to oral medications may wane over time.[86]

## Diagnostic Challenges in Dystonia

Dystonia is common in PD, as 30% of patients develop Off-state dystonia.[87] Dystonia in PD can involve focal foot dystonia, either at onset (mainly in early-onset cases) or more commonly in relation to motor fluctuations (off state dystonia). Off-state focal dystonia can respond to more frequent dosing of levodopa, or other treatments that reduce off time.[87] In comparison, upper limb dystonia may be misdiagnosed as PD. Slowness associated with dystonic movements can be confused with parkinsonian bradykinesia, while dystonic tremor, particularly if present at rest, may be misconstrued as a parkinsonian tremor.[3] Features against a diagnosis of PD include no progression of parkinsonian motor features besides tremor and dystonia, no definite features of parkinsonian bradykinesia, lack of improvement with dopaminergic therapy, and a negative dopamine transporter (DaT) scan.[88]

Dystonia may resemble essential tremor (ET), particularly in patients presenting as a cervical dystonic tremor, with or without vocal tremor.[3] Features that suggest dystonia include associated abnormal head position, a voice tremor in those who cannot change vocal pitch or strained/breathy speech, jerky tremor of the head that has a null point, response to sensory tricks, and lack of improvement from typical ET treatments (propranolol, primidone, etc.).[89]

The sudden, jerky movements of myoclonus can resemble dystonia but may also accompany dystonia in myoclonus dystonia (DYT-SCGE), where myoclonus may or may not be in

 

the same distribution as the dystonia. In contrast, essential myoclonus has no evidence of dystonia.[90] Myoclonus, which is characterized by the very rapid nature of movements, can generally be differentiated clinically from dystonia, where the movements are considerably slower and have associated directional pulling.

Tics, particularly "dystonic" tics, can be confused with dystonia. Simple motor tics commonly involve eye blinking (which can be confused with blepharospasm), while more complex tics involving the head, trunk, or limbs can be mistaken for craniocervical or limb dystonia, and both conditions may respond to botulinum toxin injections.[3] Characteristics of tic disorders that are not present in dystonia include a history of childhood tics, family history of Tourette's syndrome or a tic disorder, a premonitory urge preceding performing the movements, and partial suppressibility.[91] In addition, certain neuropsychiatric symptoms (particularly attention-deficit hyperactivity disorder/obsessive-compulsive disorder), while common in tic disorders, are infrequent in dystonia (myoclonus dystonia is an exception), while anxiety and depression are common in both, although this is nonspecific.[3]

## Treatment Principles in Dystonia

The first step is to identify the subtype and possible etiology of the dystonia syndrome, to determine if pathogenesis-directed treatments are available, such as levodopa for cases of dopa-responsive dystonia. If an underlying cause is not identified, then one should initiate symptomatic treatment with oral medications, intramuscular botulinum injections, and consider DBS. A treatment algorithm is depicted in ►**Fig. 1**.

### Pathogenesis-Directed Treatment

Although only few forms of dystonia have treatments that specifically target the underlying pathophysiological mechanisms, it is important to identify these where present, as there may be significant symptom benefit in both dystonia and other symptoms. Notable disorders for which pathogenesis-directed treatments are available include dopa-responsive dystonia, Wilson's disease, and the paroxysmal dyskinesias/dystonias.[92] Reduction of toxic substrates is important in Wilson's disease, involving oral penicillamine, trientine, and zinc therapy coupled with avoiding hepatotoxic agents, as this may prevent the progression of symptoms. Additional specific oral therapeutics include levodopa for dopa-responsive dystonia, the use of carbamazepine, and other antiseizure medications, which are highly effective in PKD (with less response to other medications in PNKD) in the paroxysmal dystonias.[92] Given the considerable symptomatic benefit in dopa-responsive cases, all childhood and young-onset dystonia patients should also be trialed on levodopa. Although this may be a good strategy in many settings, some have challenged this notion.[93]

### Symptomatic Treatment for Dystonia

As pathogenesis-guided therapies are not available for the vast majority dystonias, management of dystonia is generally symptomatic. An individualized treatment plan is typically

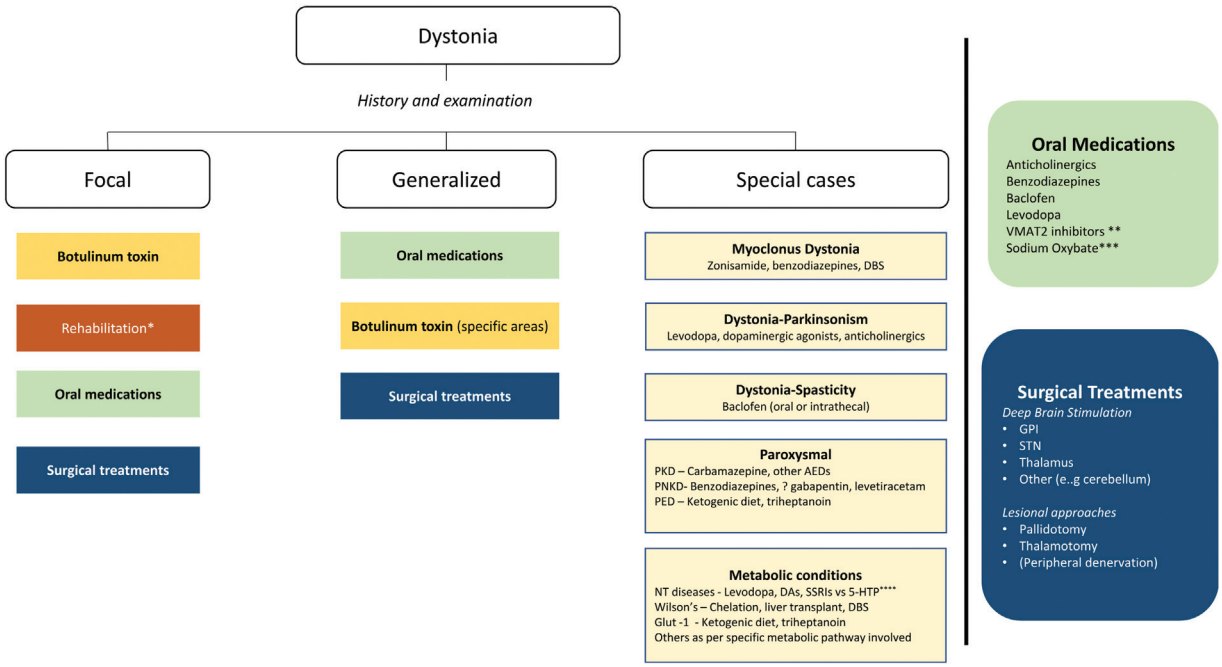


**Fig. 1** Treatment approach to dystonia. *Rehabilitation may include physical therapy, occupational therapy, and speech/swallow therapy. **VMAT2 inhibitors include tetrabenazine, valbenazine, and deutetrabenazine. Its use has been most consistently described in tardive dystonia. ***Sodium oxybate may be helpful in alcohol-responsive dystonia. ****NT diseases, neurotransmitter diseases, including dopa-responsive dystonias. AED. anti-epileptic drug; DA, dopamine agonists; SSRI, serotonin reuptake inhibitors; 5-HTP, 5-hydroxytryptophan; DBS, deep brain stimulation; GPi, globus pallidus internus; STN, subthalamic nucleus; PED, paroxysmal exercise-induced dyskinesia/dystonia; PKD, paroxysmal kinesigenic dyskinesia/dystonia; PNKD, paroxysmal nonkinesigenic dyskinesia/dystonia; SPR, sepiapterin reductase; VMAT2, vesicular monoamine transporter 2.

 

guided by personal experience and successive empirical medication trials; as other than for botulinum toxin injections, there is a dearth of double-blind, placebo-controlled trial data.

## Rehabilitation Strategies in Dystonia

Rehabilitation is a useful nonpharmacological management strategy for dystonia and includes physical therapy (PT), occupational therapy (OT), and speech and language pathology (SLP). In complex cases, rehabilitation can be guided by physical medicine and rehabilitation specialists (physiatry), in tandem with neurologists. PT and OT can help leverage sensory tricks and improve function through retraining or other techniques. Rehabilitation approaches in task-specific dystonia (mainly involving OT for focal hand dystonia) include movement practice, sensory reeducation, exploiting sensory tricks, and biofeedback training, combined with sensorimotor training and the use of compensatory strategies.[94,95] Neck PT has been used as an adjuvant for cervical dystonia, with strategies including electromyography (EMG) biofeedback, muscular elongation, postural exercises, and electrical-based therapy, and the use of a neck brace for mechanical correction, although results are varied.[96] Sensorimotor retraining (such as practicing picking up objects from a container of rice or dried pulses, or using Braille), and motor imagery may be helpful in the rehabilitative treatment of focal dystonia.[97,98] Biofeedback can include the use of mirror therapy or the use of EMG.[99,100] Finger or foot splinting can be helpful, although there may be discomfort from the dystonic movement fighting the constraint. In laryngeal and/or oromandibular dystonia, SLP is essential to improve speech intelligibility, and includes behavioral and compensatory strategies, as well as swallow therapy to provide strategies and advice for safe swallowing.[101]

## Chemodenervation for Dystonia

Since its introduction in the 1980s, the use of botulinum has been the mainstay of treatment for focal forms of dystonia. In 1987, Jankovic and Orman produced the first reports of efficacy in a landmark double-blind controlled study in cervical dystonia and blepharospasm.[102] Subsequently, all forms of focal dystonia are now routinely treated with botulinum toxin injections, including the masticatory muscles and tongue in oromandibular dystonia, and the vocal folds in laryngeal dystonia.[103–106] Two serotypes are used: serotype A includes onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin), while the sole form of serotype B is rimabotulinumtoxinB (Myobloc). It is important to remember that other than onabotulinum toxin and incobotulinum toxin which have equivalent units and doses, the other formulations are not interchangeable and transitioning from one form to the other must be done carefully. Although a 12-week duration between doses is typical (often driven by insurance coverage), many patients experience a shorter duration of efficacy, although some patients may require less frequent injections.[107,108]

The efficacy and safety of botulinum toxin depends on the appropriate selection of the muscles driving the dystonic contractions and dosage. To ensure the correct muscles are injected, the use of ancillary measures have become commonplace, including EMG guidance, ultrasound, electrical stimuation, or a combination of these approaches, such as is required for the precise localization required for writer's cramp and particularly musician's dystonia, where only a single finger muscle may need to be injected.[109]

Despite sustained efficacy in many, patients stop botulinum toxin therapy for various reasons, including inadequate efficacy and adverse effects, convenience (every 3-month injections) and cost of treatment.[110,111] A practical method for assessing resistance to the effects of botulinum toxin is the "frontalis test", where clinicians inject ~10 units unilaterally in the procerus and assess for relaxation (loss of the ability to furrow the brow) 2 to 3 weeks later.

## Oral Pharmacotherapy for Dystonia

Oral medications are generally considered in multifocal/generalized dystonia and in combination with botulinum toxin injections in select cases of segmental and focal dystonia. Benefit of such oral medications is typically only moderate at best, although can vary depending on the type of dystonia.

Dopaminergic therapy, most commonly levodopa, is the treatment of choice for dopa-responsive dystonia.[112] However, this may also be beneficial in combined dystonia parkinsonism, although typically with a less robust response than is seen in PD.[113] Anticholinergic therapy (e.g., trihexyphenidyl or benztropine) is mainly used in multifocal/generalized and less often in segmental dystonia.[114] Of these, trihexyphenidyl is the most effective (response in 71%), although this high response declines over time,[115] with at least a moderate benefit in 50% of children and 40% of adults.[116] Anticholinergic side effects, including dry mouth, constipation, blurred vision, cognitive changes, and drowsiness, substantially limit their use in older patients.[117]

Baclofen is a GABAb autoreceptor agonist, typically used for the treatment of spasticity.[114] At relatively low doses, it can provide some relief to dystonia affecting the craniofacial muscles. However, its sedating side effect typically limits the maximum tolerated daily dose.

Benzodiazepines (particularly clonazepam, given its longer half-life) are also commonly used as adjunctive treatment, for their muscle relaxant and other properties, such as the treatment of myoclonus in the myoclonus dystonias.[116] There may also be a synergistic benefit in combination with anticholinergic medications; however, sedation, particularly in the older person, limits their use. It is also important to acknowledge to patients the risks of potential abuse (11% in a cohort of cervical dystonia patients),[118] tolerance, and withdrawal.

Sodium oxybate is a controlled drug generally indicated in alcohol-responsive cases,[119,120] such as myoclonus dystonia and laryngeal dystonia, where there is evidence of efficacy following open-label trials.[111,121] Zolpidem, a nonbenzodiazepine hypnotic medication, has been reported to improve blepharospasm and other forms of dystonia, generally at doses between 5 and 20 mg/day.[122]

 

**Table 4** Predictors of deep brain stimulation outcome in dystonia

| Positive outcome | Negative outcome |
|---|---|
| • Isolated, segmental, or generalized dystonia<br>• Younger age of onset<br>• No other significant medical comorbidities<br>• Mobile dystonia<br>• Normal MRI of the brain<br>• Shorter symptom duration<br>• DYT-TOR1A and other genetic dystonias with robust efficacy data | • Acquired/complex dystonia<br>• Older age of onset<br>• Significant medical, cognitive/neuropsychiatric comorbidities<br>• Prior brain surgery<br>• Fixed dystonia or contractures<br>• Abnormal MRI of the brain<br>• Long symptom duration<br>• Genetic dystonias without data for efficacy (e.g., ATP1A3)<br>• Presence of fixed contractures<br>• Prior brain surgery<br>• Concomitant spasticity or ataxia |

Abbreviation: MRI, magnetic resonance imaging.

### Deep Brain Stimulation for Dystonia

DBS of the globus pallidus interna (GPi) was approved for dystonia in 2003. Indications for DBS include severe medication-refractory generalized or segmental dystonia,[123,124] with high-level Class 1 evidence from large-scale randomized clinical trials, as well as some forms of focal dystonia, including medication-refractory cervical dystonia.[125] Focal dystonias for which there is less evidence of efficacy include Meige syndrome.[126,127]

The effectiveness of DBS depends on the careful selection, based on the genetic dystonia diagnosis, age, and dystonia subtype. Isolated generalized and more widespread dystonia subtypes tend to have a greater response rate, with better efficacy in DYT-TOR1A dystonia, younger age at surgery, shorter disease duration, and higher dystonia severity.[128] Combined dystonias may also respond well to DBS, particularly DYT-*KMT2B*, DYT-SGCE, and DYT-PARK-TAF1, with variable efficacy in CHOR/DYT-*ADCY5*, DYT-*GNAL*, and DYT-*THAP1*, infrequent efficacy in DYT-*PRKRA* and no significant response in DYT/PARK-*ATP1A3*.[128] Predictors of DBS outcome in dystonia are shown in ►**Table 4**.

### Treatment of Paroxysmal Dyskinesias

A generic therapy relevant for all forms of the paroxysmal dystonias involves avoiding triggers. In PKD, low-dose carbamazepine (50–200 mg/day) can be highly effective. Other antiseizure medications that may be effective in PKD include oxcarbazepine, phenytoin, and lacosamide (50–100 mg/day), with possible reported benefit with valproic acid, lamotrigine, levetiracetam, or topiramate.[84] In PNKD, treatment is much less effective than PKD and includes low-dose benzodiazepines, gabapentin, and levetiracetam.[129] In PED, the mainstay of treatment involves dietary glucose modification with the ketogenic diet, with concomitant L-carnitine, while triheptanoin (an odd-chain fatty acid) resulted in a dramatic decrease in PED attacks in an open-label trial.[130] There are limited data for partial benefit with levodopa, trihexyphenidyl, and benzodiazepines in PED.[84] There is a paucity of evidence for surgical management of the paroxysmal dystonia/dyskinesias.

## Conclusion and Future Directions

Dystonia is a clinical diagnosis, made based on history, observation, and direct examination. Treatment depends on patient age, diagnosis, and dystonia distribution, and is individualized, consisting of rehabilitation, botulinum toxin injections, oral pharmacotherapy, and DBS or focused ultrasound. However, the greatest advances have been in the field of dystonia genetics, with many new genes discovered over the past 20 years. Natural history studies of each dystonia-causing mutation, that include response to treatment, may help determine which treatments are likely to be most effective for individuals with specific gene mutations.

Advancements are also being made with botulinum toxins. Newer botulinum toxins are being investigated for several indications, such as glabellar lines, post-stroke upper limb spasticity, and dynamic equinus foot deformity in children with cerebral palsy.[131] In a phase 2, open-label dose-escalation study, daxibotulinumtoxinA demonstrated clinical and objective improvement of symptoms in individuals with cervical dystonia with a longer duration of effect, which may allow for less frequent injections and a lower cost to patients.[132] Results from the Phase 3 trial demonstrated safety and efficacy.[133] Promising new agents on the horizon that require additional human studies include ritonavir and VU6028418.[134,135] Ritonavir, which is FDA approved to treat HIV, is hypothesized to act via promoting the integrated stress response within cells, which has been shown to be abnormal in DYT1 cell lines.[134] VU6028418, a highly selective M4 muscarinic acetylcholine receptor antagonist, may have less side effects than trihexyphenidyl.[135] Thus, it is likely that new oral agents and different serotypes of botulinum toxin will become available in the coming years.

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Conflict of Interest
None declared.

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