REVIEW ARTICLE

The Dystonias

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CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

CITE AS:
CONTINUUM (MINNEAP MINN) 2019;25(4, MOVEMENT DISORDERS): 976–1000.

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RELATIONSHIP DISCLOSURE:
Dr Jinnah has received personal compensation for serving on the advisory boards of and as a consultant for Abide Therapeutics, Inc; Allergan, Inc; CoA Therapeutics; the International Neurotoxin Society; the International Parkinson and Movement Disorders Society; Medtronic; the Parkinson's Foundation; Psyadon Pharmaceuticals Inc; Retrophin, Inc; and Saol Therapeutics. Dr Jinnah has received grant support from the Benign Essential Blepharospasm Research Foundation, Cavion, Cure Dystonia Now, the Dystonia Study Group, Ipsen Group, National Institutes of Health (NIH), and Retrophin, Inc. He also is principle investigator for the Dystonia Coalition, which receives the majority of its support through NIH grant TR001456 from the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences and previously received support through grant NS065701 from the National Institutes of Neurological Disorders and Stroke. The Dystonia Coalition has received additional material or administrative support from industry sponsors (Allergan, Inc and Merz Pharmaceuticals) as well as private foundations (the American Dystonia Society,
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ABSTRACT

PURPOSE OF REVIEW: This article provides a summary of the state of the art in the diagnosis, classification, etiologies, and treatment of dystonia.

RECENT FINDINGS: Although many different clinical manifestations of dystonia have been recognized for decades, it is only in the past 5 years that a broadly accepted approach has emerged for classifying them into specific subgroups. The new classification system aids clinical recognition and diagnosis by focusing on key clinical features that help distinguish the many subtypes. In the past few years, major advances have been made in the discovery of new genes as well as advances in our understanding of the biological processes involved. These advances have led to major changes in strategies for diagnosis of the inherited dystonias. An emerging trend is to move away from heavy reliance on the phenotype to target diagnostic testing toward a broader approach that involves large gene panels or whole exome sequencing.

SUMMARY: The dystonias are a large family of phenotypically and etiologically diverse disorders. The diagnosis of these disorders depends on clinical recognition of characteristic clinical features. Symptomatic treatments are useful for all forms of dystonia and include oral medications, botulinum toxins, and surgical procedures. Determination of etiology is becoming increasingly important because the number of disorders is growing and more specific and sometimes disease-modifying therapies now exist.

INTRODUCTION

The dystonias are a diverse family of disorders that share an underlying phenomenon of excessive contractions of specific muscle groups leading to abnormal movements.[1] Any region of the body can be affected, and the overt manifestations depend on the severity and distribution of muscles involved. In its mildest forms, abnormalities appear as slight distortions of otherwise normal movements. In patients who are more affected, abnormal movements have a more obvious appearance of cramping, stiffening, jerking, or twisting. The most severe cases of dystonia are associated with fixed abnormal postures or joint deformities with severe disability.

The causes of dystonia are similarly diverse.[2] Some types of dystonia are associated with overt neuropathologic abnormalities of the brain that can be detected by neuroimaging or postmortem histopathologic studies, such as focal lesions or degenerative changes. Some types of dystonia are acquired whereas

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others are inherited. Most cases are idiopathic with no apparent cause. This article describes how to recognize the varying manifestations of dystonia, how the many different subtypes are grouped, the causes and diagnostic evaluation for the more common subtypes, and current treatment strategies.

DIAGNOSIS OF DYSTONIA

Dystonia is easy to recognize in its most classic expressions, in which patients exhibit twisting movements and abnormal postures affecting many regions of the body. Less severe expressions are often misdiagnosed. Several studies have revealed that the average time from onset of symptoms to diagnosis can take many years, even for the most common subtypes (TABLE 5-1).[3–7] Part of the reason for delayed diagnosis is that the definition of dystonia and the many syndromes included under this umbrella term have evolved over the years.

Definition of Dystonia

The definition of *dystonia* has evolved considerably since it was first described more than 100 years ago. In 2013, an international panel of experts agreed to the following working definition:

> Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.[1]

One of the main reasons for delayed diagnosis is lack of appreciation that abnormal movements in dystonia can fall into two broad categories that often overlap. They can be slow and twisting and sometimes with abnormal postures that appear to be fixed, such as the abnormal postures and slow but repetitive deviations of the head in cervical dystonia or the overt twisting of a foot. Alternatively, dystonic movements can be rapid and jerky, including the periocular spasms of blepharospasm, voice breaks of laryngeal dystonia, dystonic tremor, and myoclonic dystonia. In some patients, movements may be rapid and

Diagnostic Delays in Dystonia[a] TABLE 5-1

Type of Dystonia	Location of Study	Years to Diagnosis
Adult-onset focal dystonias	Australia[3]	3.8
Adult-onset focal dystonias	Canada[4]	6.4
Blepharospasm	Italy[5]	4.8
Cervical dystonia	Italy[5]	7.1
Cervical dystonia	United States[6]	3.7
Hand dystonia	Italy[5]	10.1
Laryngeal dystonia	United States[7]	4.4

[a] This table describes the average length of time from symptom onset to diagnosis of dystonia.

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repetitive, resembling tremor. In these cases, the term *dystonic tremor* is sometimes used. Although the slow and twisting movements are readily recognized, the rapid and repetitive movements are often missed.

Whether dystonic movements are slow or fast, several clues aid the recognition. The first clue is that abnormal movements tend to be patterned, which refers to a recurrent quality of sameness. This quality helps differentiate dystonia from chorea, in which movements are more random. Motor tics can also be patterned, but associated premonitory sensations occur, and abnormal movements can be voluntarily suppressed. Dystonic movements usually lack premonition and cannot be suppressed by will alone.

Another helpful clue is that dystonic movements tend to be triggered or worsened by voluntary action. In some cases, dystonia emerges only with specific tasks. For example, patients with writer's cramp may have cramping of hand muscles and abnormal postures or jerking with writing, yet there is no difficulty with other fine motor skills such as brushing teeth, eating with a fork and knife, or buttoning a shirt. Patients with musician's dystonia may have trouble playing one instrument but not another. Even when dystonias are not task specific, most tend to be exaggerated by voluntary action.

Although not always present, identification of a geste antagoniste (sensory trick) also can be a very helpful clue because it is unique to dystonia.[8] Typical examples include touching the lower face in cervical dystonia, touching the upper face in blepharospasm, or putting a toothpick in the mouth in oromandibular dystonia. Patients should always be asked if they can do anything to suppress their abnormal movements because these tricks can be very odd and patients are sometimes reluctant to mention them.

Finally, like many other neurologic disorders, it is useful to remember that stress and fatigue tend to worsen dystonia. Increased frequency of depression and anxiety occurs with many types of dystonia.[9] These issues frequently lead to misdiagnosis of dystonia as stress-induced or a nervous habit.

Clinical Evaluation

The many types of dystonia are grouped according to two main axes: a clinical axis and an etiologic axis (FIGURE 5-1). The clinical history and examination (axis I) should address four dimensions that include age at onset, body region affected, specific temporal features, and whether associated clinical problems are present.[1] Age at onset is important because subtypes that emerge in infancy

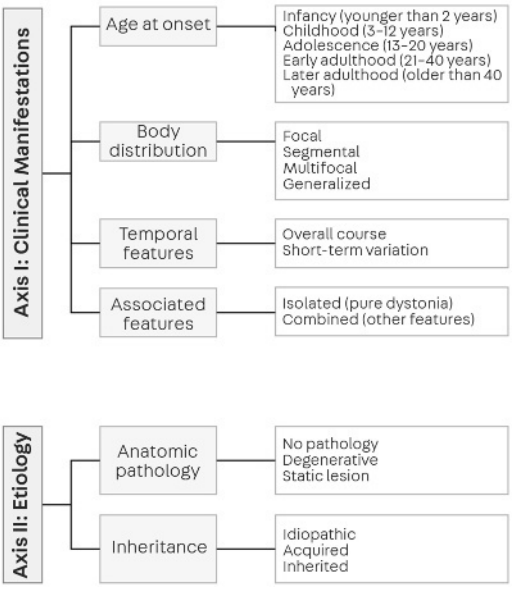

FIGURE 5-1

Classification of the dystonias. The many types of dystonia are classified according to two independent axes. One axis relates to clinical features, and the other relates to etiology.

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are most commonly due to inherited metabolic disorders, those that arise in later childhood or adolescence are more often inherited isolated or degenerative dystonias, and those that arise in later adulthood are most often idiopathic. Early-onset cases often start in one body region and progress to broader distributions over months or years, whereas late-onset cases tend to have a slower and more limited progression.

Almost any region of the body can be affected, either alone or in different combinations. The focal dystonias affect a single body region, segmental dystonia affects two or more contiguous body regions, and multifocal dystonia affects two or more noncontiguous regions. Hemidystonia can be viewed as a special subtype of generalized dystonia where half of the body is involved, usually at least the arm and leg on one side. Generalized dystonia occurs when the trunk is affected along with at least two other body regions.

Temporal aspects refer to variations over time. Dystonia can emerge over a short period of time and remain relatively static thereafter. Dystonia can also progress rapidly over a few hours or days, it can progress more slowly over many years, or it can progress in a stepwise fashion. Shorter-term variations also exist, such as diurnal worsening in the evening in dopa-responsive dystonia, or episodic attacks on a relatively normal baseline in paroxysmal dyskinesias.

Finally, it is important to determine if dystonia occurs in isolation or if it is combined with other clinical problems. The term *isolated dystonia* is used when no other relevant clinical problems apart from tremor occur, which is observed in approximately half of patients with dystonia. The term *combined dystonia* refers to syndromes in which dystonia is combined with other clinical problems. It may be combined with other movement disorders, such as parkinsonism or ataxia, with other neurologic problems, such as neuropathy or retinopathy, or with systemic issues, such as liver or kidney disease.

Laboratory Investigations

Each of the four clinical dimensions described above is important for describing a syndromic pattern, which helps guide laboratory investigations to delineate etiology, which falls in axis II (FIGURE 5-2). Universal algorithms for laboratory investigations in the dystonias are challenging because of the remarkable heterogeneity of clinical manifestations and causes. A comprehensive review described more than 100 dystonic disorders organized into 18 tables based on specific clinical features.[2] Although several different algorithms have been proposed,[10–14] none is complete. Following are some general guidelines for laboratory investigations.

For dystonias that first emerge in later adulthood (patients older than 40 years of age), laboratory investigations depend on body distribution, whether additional neurologic features are present, and temporal aspects. For the most common adult-onset focal or segmental dystonias, such as cervical dystonia or blepharospasm, diagnostic testing is usually unrevealing. For laryngeal dystonia, laryngoscopy is recommended to rule out structural defects of the vocal apparatus.[15] For the less common adult-onset cases with hemidystonia or generalized dystonia, neuroimaging can be useful to reveal a structural cause. Neuroimaging is also useful in patients with adult-onset dystonia with rapid or severe progression of symptoms or if dystonia is combined with other neurologic features, such as parkinsonism or ataxia. For

KEY POINTS

- Dystonic movements are not always slow; they can be rapid or jerky, or resemble tremor.
- Dystonic movements tend to be patterned, not random.
- Dystonic movements are often triggered or worsened by voluntary muscle activity.
- Identification of a geste antagoniste (sensory trick) can be a very helpful clue because it is unique to dystonia and is important to ask patients about.
- The history and examination of patients with dystonia should focus on four areas: body region affected, age at onset, temporal features, and ancillary neurologic problems.

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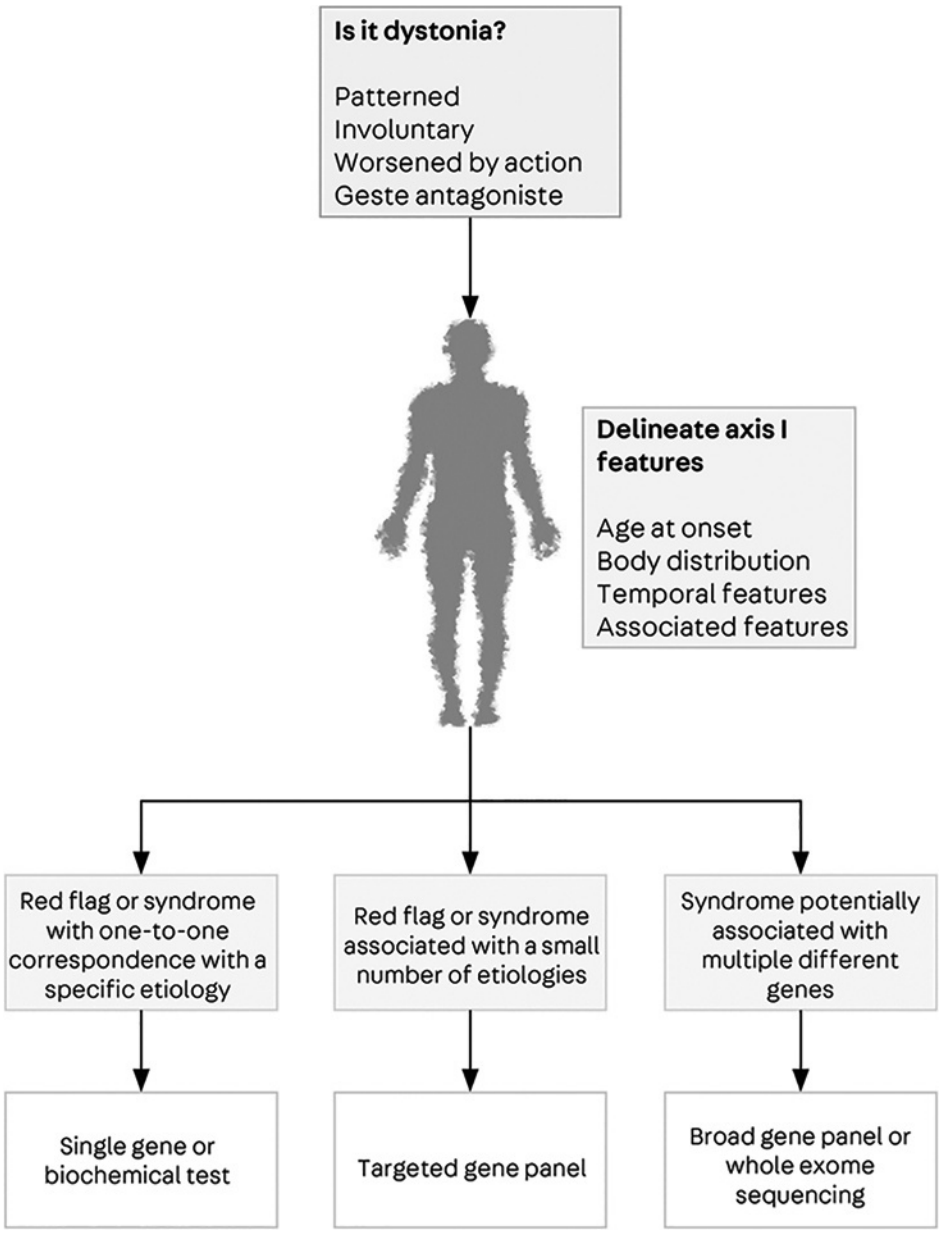

FIGURE 5-2
Workup of dystonia. The evaluation begins with clinical evaluation according to four main clinical domains. The resulting syndromic pattern can be used to guide the approach to the diagnostic workup.

most cases that emerge in later adulthood, genetic testing is not usually conducted unless multiple family members are affected or a specific syndromic pattern leads to suspicion for an inherited disorder. EEG is not usually conducted unless dystonia appears in paroxysmal attacks. EMG is not needed unless a neuromuscular disorder that may resemble dystonia is suspected, such as myotonia or stiff person syndrome.

For dystonias that first emerge at an earlier age (in patients younger than 40 years), some laboratory investigations are almost always valuable.[2] The

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diagnostic strategy for this group has evolved in the past few years, with multiple conflicting recommendations from different experts. Most experts recommend neuroimaging because it can provide clues to guide diagnostic testing. Beyond this step, strategies vary. Some experts advocate a "red flag" approach, in which diagnostic testing is guided by the identification of telltale features from the medical history, clinical examination, or neuroimaging. Examples of red flags include the corneal Kayser-Fleischer ring of Wilson disease or the "eye of the tiger" sign on MRI for neurodegeneration with brain iron accumulation. Although this strategy can be useful when such telltale features are found, it does not provide an adequate approach in all cases. Red flags are sometimes missing where they are expected, many disorders lack red flags, and it is difficult even for experts to remember all the red flags.

A related strategy is to delineate a group of clinical abnormalities that form a recognizable syndromic pattern to guide diagnostic testing. An example of this is Lesch-Nyhan disease, where patients present with early-onset generalized dystonia, intellectual disability, tendencies toward self-harm, and elevations of serum uric acid.[16,17] This syndrome is unique; it is associated only with the *HPRT1* gene, so single gene or enzyme testing is efficient.[18] However, many other disorders present with overlapping syndromes with many causes. It can be challenging even for experts to remember all syndromes, and partial syndromes are hard to recognize. For almost all of the classic phenotypes described for inherited disorders of children, adult-onset variant forms with partial syndromes may occur. Furthermore, syndromic patterns are sometimes misleading. An example involves the *ATM* gene, which is classically associated with ataxia-telangiectasia in children. However, mutations in this gene can sometimes cause isolated focal or generalized dystonia, sometimes in adults and sometimes without telangiectasias.[19] In the era of shotgun genetic testing that may involve whole exome sequencing or large multigene panels, unexpected results are common.[20,21]

A third strategy sometimes recommended is focusing laboratory investigations specifically on disorders for which specific treatments exist. The rationale for this strategy is that obtaining a definitive etiologic diagnosis for dystonia often does not change clinical management because most are managed symptomatically. According to this strategy, laboratory testing should focus only on a smaller number of treatable disorders, such as Wilson disease, for which specific treatments are available. This strategy is unwise. Even when the cause does not have a specific treatment, many patients and families find that obtaining a definitive etiologic diagnosis is useful for ending an often long diagnostic odyssey.[20,22–24] The information also provides valuable information for counseling regarding the prognosis for the individual affected and the potential risk for family members. A more important weakness of this strategy is that the number of disorders with specific treatments has been growing rapidly in recent years.

A recent review summarized more than 30 inherited disorders with specific therapeutic interventions, and dystonia occurred in more than half of those disorders.[25] In these disorders, dystonia often is part of a more complex picture with multiple neurologic and systemic problems. However, sometimes dystonia is the sole initial presentation, and the diagnosis is delayed because the whole syndrome has not yet evolved. At the same time, early treatment often is critical to prevent permanent neurologic sequelae. The list of treatable disorders has

KEY POINTS

- For the most common focal dystonias that emerge after 40 years of age, laboratory investigations are usually not needed.
- For any dystonia that emerges in a child or young adult, laboratory investigations are guided by the history and examination.
- For almost all classic inherited dystonic disorders in children, late-onset cases or less severe cases are known to occur in adults.
- Elucidating etiology is important because specific treatments are available for several types of dystonia.

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TABLE 5-2

Selected Dystonia Syndromes and Their Genes[a]

Isolated (Relatively Pure Dystonia)

- ***TOR1A***
  - Typical onset in arm or leg in childhood with generalized spread; other onset sites or onset in adults may occur
- ***THAP1***
  - Typical onset in adolescents or young adults with segmental pattern involving face, neck, larynx, and upper limbs
- ***ANO3***
  - Typical onset in adults with segmental pattern involving neck, larynx, and upper limbs; coarse tremor is common
- ***GNAL***
  - Typical onset in adults with segmental pattern involving neck, larynx, and upper limbs

Combined (Other Relevant Features)

- **Dopa-responsive dystonia phenotypes**
  - Metabolic phenotypes start in childhood; often combined with mild parkinsonism; most commonly caused by *GCH1*, less commonly *TH*, *SPR*, and *PTS*; may resemble early-onset degenerative Parkinson disease due to mutations in *PRKN* and *PINK1*
- **Paroxysmal dyskinesia phenotypes**
  - Typical onset in childhood; often combined with chorea, tremor, and other movements; different subtypes are triggered by sudden action, lengthy exercise, or stress; genes include *PRRT2*, *MR1*, *SLC2A1*, and others
- **Rapid-onset phenotypes with dystonia**
  - Typical onset in childhood or adolescents following physical or psychological stress; causes include *ATP1A3*, *GCDH*, *MUT*, *PCCA*, *PCCB*, and *SLC19A3*
- **MRI phenotypes with metal deposition**
  - Typical onset in childhood or early adults with parkinsonism and characteristic MRI; copper accumulation occurs with *ATP7B*, manganese accumulation with *SLC30A10* or *SLC39A14*, iron accumulation with *PANK2*, *PLA2G6*, *WDR45*, and others
- **Dystonia phenotypes with myoclonus**
  - Typical onset in childhood with dystonia in neck or upper limbs; myoclonus may predominate; caused by *SGCE*, *KCTD17*, and *RELN*
- **Dystonia phenotypes with ataxia**
  - Onset ranges from early childhood to later adulthood depending on subtype; many potential causes including *ATM*, *CTX*, *NPC*, *POLG*, and several spinocerebellar ataxias

MRI = magnetic resonance imaging.

[a] This table does not contain a complete listing of all dystonia syndromes and their genes. It includes the more common subtypes, those with red flags or characteristic syndromes, those that are treatable, or those with substantial recent progress.

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been growing each year, making it challenging to know what disorders should be tested.

In view of these limitations of traditional strategies for laboratory investigations, there is a growing trend toward the greater use of broad dystonia gene panels or whole exome sequencing. The red flags and syndromic strategies are useful only when the clinical clues point specifically to a single or small number of potential diagnoses to target. Serial genetic testing, starting with the most likely genes, should be avoided because it is frustrating and more expensive than ordering a larger panel. If a dystonia gene panel is used, it is important to know what it covers. Gene panels are not standardized across testing laboratories. Some include as few as 12 genes, whereas others include more than 100, often at the same cost. Even for large panels, current costs are in the same range as brain MRI. A potentially useful approach for using the various diagnostic strategies is shown in FIGURE 5-2, and some example phenotypes are shown in TABLE 5-2.

Even when an etiologic diagnosis cannot be reached, it is important to follow patients because new problems may arise that point to the cause. For example, some patients may present with what appears to be an isolated focal dystonia of the hand or foot, but signs of parkinsonism may develop months or years after onset. In an older adult, this evolution may point to Parkinson disease, where 10% to 15% of patients present with isolated dystonia of the arm or leg.[26] Alternatively, this evolution could point to one of the atypical parkinsonian disorders for which the frequency of dystonia is even higher.[27] In a child or young adult, this evolution may point to one of many inherited metabolic or degenerative disorders in which dystonia and parkinsonism are combined.[28]

KEY POINT

● Isolated dystonia may be the initial manifestation for neurologic disorders typically associated with more complex syndromes.

CAUSES OF DYSTONIA

There have been enormous advances in elucidating the varied causes of dystonia and in understanding the different biological mechanisms involved. This section summarizes the major conceptual advances in three areas: genetic, physiologic, and neuroanatomic.

Genetic Basis

Historically, most genes have been identified by a laborious process that involved collecting large families, correlating the disease phenotype with known genetic markers spread across the genome, and then sequencing DNA in the chromosomal region with the best links between the phenotype and the known markers. To aid this process of gene discovery, nomenclature was developed that was based on linkage to chromosomal locations, or *loci*. Disorders with dystonia were given the prefix DYT followed by a number, such as DYT1, DYT2, DYT3, and so on.

This nomenclature has numerous flaws.[29] In some cases, different DYT loci ultimately were linked with the same gene. In other cases, multiple genes were linked with the same DYT locus. Several DYT entries were found to be erroneous or were never verified. The nomenclature also was clinically misleading because it incorrectly implied that dystonia was a significant feature of any disorder with a DYT label. The most serious drawback of this nomenclature was that it was incomplete. It did not include dystonia genes that were found before the DYT convention was established. Wilson disease

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is one of many examples that was never included in the DYT lists despite the fact that dystonia occurs in nearly all cases with neurologic involvement. In fact, more than 100 inherited conditions exist in which dystonia may be a major feature, a presenting feature, a dominant feature, or part of a more complex syndrome.[2] Only a small fraction of these disorders was assigned a DYT label.

The next generation of genetic methods has led to major changes in our approach to identifying genes for dystonia. A linkage-based nomenclature is no longer central to gene discovery, and new genes are no longer consistently being assigned DYT labels. Instead, a new nomenclature has been proposed.[29] In the new nomenclature, the number is replaced by the gene name. For example, *TOR1A*-associated dystonia (DYT1 according to the old nomenclature) would be called DYT-*TOR1A*. Additionally, when the phenotype is mixed, multiple prefixes may be combined, such as DYT for dystonia, PARK for parkinsonism, or SCA for spinocerebellar ataxia. For example, dopa-responsive dystonia (DYT5 in the old nomenclature) would be called DYT/PARK-*GCH1*, DYT/PARK-*TH*, or DYT/PARK-*SPR*. The new convention more accurately acknowledges the frequent occurrence of parkinsonism with dystonia in dopa-responsive dystonia as well as at least three different causative genes.

This new nomenclature is still evolving. It requires expertise in neurogenetics and can be challenging to apply in routine clinical practice. For the practicing neurologist, it is most useful to group genes by pattern of inheritance (TABLE 5-3). The pattern of inheritance is important for genetic counseling, and knowing the gene has implications for mechanism-specific treatments, such as for Wilson disease. However, it is important to recognize that some of the most common dystonia genes are dominant but inherited with reduced penetrance (eg, *GCH1, TOR1A, THAP1*). This phenomenon may make inheritance patterns difficult to recognize. In addition, considerable phenotypic variation can occur in individual members of the same family with the same genetic defect. For example, individual members of the same family can have severe childhood-onset generalized dystonia, adolescent-onset segmental dystonia, or adult-onset focal dystonia. This phenomenon can make it

TABLE 5-3 **Classification of Genes by Pattern of Inheritance**[a]

Pattern of Inheritance	Genes
Autosomal dominant	*ANO3, ATP1A3, CIZ1, GCH1, GLUT1, GNAL, PNKD, PRRT2, SCA3, SGCE, SLC2A1, THAP1, TOR1A, TUBB4*
Autosomal recessive	*AADC, ATP7B, COL6A3, CYP27A1, GCDH, HPCA, KMT2B, NPC1* or *NPC2, PCCA* or *PCCB, PLA2G6, PRKRA, SLC19A3, SLC39A14, SPR, TH*
X-linked	*ARX, HPRT, MECP2, PLP1, TAF1, TIMM8A, WDR45*
Mitochondrial	*MT-ATP6, MT-CO3, MT-ND1, MT-ND4, MT-TL1, MT-TK*

[a] These patterns can be challenging to recognize when families are smaller and because several dominantly inherited dystonia genes have partial penetrance.

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challenging to identify individual family members who may have the same disorder. Some of the most common or recently discovered genes and their typical phenotypes are summarized in TABLE 5-2 and in multiple recent reviews.[20,30,31]

Physiologic Basis

Historically, physiologists emphasized a cardinal defect that involved co-contraction of antagonistic muscle groups in dystonia. However, co-contraction of opposing muscles is not universal. Furthermore, co-contraction of opposing muscles is not specific for dystonia because it can be seen in other situations, such as stiff person syndrome, psychogenic dystonia, and voluntary isometric contraction. Instead, the cardinal physiologic defect in dystonia is excessive contraction of muscles. This overcontraction may take the form of excessive force, unwanted repetitive contractions, or spread of contractions to nearby muscles. When this spread involves opposing muscles, then co-contraction of agonist and antagonist muscles can occur.

The physiologic basis for overcontraction of muscles is not yet understood, and three main mechanisms have been proposed.[32] One mechanism involves a loss of inhibitory influences in the central nervous system. This loss of inhibition has been described for many types of dystonia. Another mechanism involves abnormalities of sensorimotor integration. Although overt sensory deficits are not common, many studies have revealed subclinical defects in spatial and temporal somatosensory discrimination thresholds for several types of dystonia. A third mechanism is maladaptive plasticity, which again has been described for many types of dystonia.

The molecular and cellular abnormalities responsible for these physiologic defects have been the targets of intense scrutiny. The large number of genetic and nongenetic causes for dystonia span very diverse biological processes (TABLE 5-4).[20,30,31] Inherited disorders with dystonia include defects in metabolism (amino acids, carbohydrates, energy, lipids), heavy metal storage (copper, iron, manganese), neurotransmitter defects, dysregulation of ion channels (sodium, potassium, calcium), abnormal gene processing and

Grouping of Dystonia Genes by Related Biological Pathways[a] TABLE 5-4

Biological Process	Genes
Dopamine signaling	*GCH1, TH, SPR, PTPS, AADC, VMAT2, PARKIN, PINK1, HPRT, GNAL*
Cation transporters	*ATP1A3, ANO3, CACNA1A, CACNA1B, HPCA, KCTD17*
Heavy metal accumulation	*ATP7B, PANK2, PLA2G6, SLC30A10, SLC39A14*
Metabolic abnormalities	*GLB1, HEXA, HEXB, HPRT1, NPC1, NPC2, SLC19A3*
Mitochondrial dysfunction	*MT-ATP6, MT-CO3, MT-ND1/MT-ND4, MT-TL1, MT-TK, PLA2G6, POLG, TIMM8A*
Gene regulation	*APTX, ATM, PNKP, SETX, TAF1, THAP1*

[a] Dystonia genes relate to numerous biological processes, and only a few of the main genes are shown.

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transcription, degenerative disorders, and others. It seems unlikely that all types of dystonia are caused by a single molecular or cellular process. Instead, it is more likely that these processes converge to affect specific neuroanatomic pathways responsible for dystonia.

Acquired processes that may cause dystonia include vascular, infectious, immunologic, or structural; drugs or toxins may also cause dystonia. Two acquired forms of dystonia are especially important to recognize. The first is tardive dystonia caused by dopamine-receptor–blocking drugs such as neuroleptics or metoclopramide. These drugs more commonly provoke repetitive oral and lingual movements of tardive dyskinesia. However, some patients develop predominantly dystonic manifestations. The most common patterns involve the craniocervical regions or backward arching of the trunk or neck. The second acquired form of dystonia is functional (psychogenic) dystonia, which can closely mimic organic dystonia. Features suggestive of functional dystonia include nonpatterned movements (tendency to change body regions or primary muscles involved over time), abrupt onset, attenuation with distraction, or other unusual accompanying features (CASE 5-1).

Neuroanatomic Basis

Historically, abnormalities in the basal ganglia have been considered the cause of all forms of dystonia.[33] In fact, very good evidence suggests that the defects in the basal ganglia can cause dystonia. One example is dopa-responsive dystonia, which can be caused by inherited defects that affect the production of dopamine

CASE 5-1

A 56-year-old woman was referred for possible neuromodulation of generalized dystonia because of uncontrolled twisting movements and jerking of many parts of her body. Before this referral, previous trials of several medications including carbidopa/levodopa and anticholinergics had not been successful in alleviating her symptoms.

These movements started suddenly one morning and initially affected one side of her face. Days later, the movements switched to the other side of her face. Weeks later, both her arms began to twist, jerk, and flail. The arm symptoms were intermittent, and occasionally her trunk and legs were involved. Examination revealed obvious twisting and jerking movements in many body regions. However, the movements were not patterned and tended to change in quality and move from one region to another. The movements stopped transiently when she was asked to write.

COMMENT

This patient may have functional (psychogenic) dystonia because of the abrupt onset, nonpatterned nature of her movements over weeks and even over the course of the examination, and distractibility. Neuromodulation surgery should not be recommended for functional dystonia. Although oral medications can sometimes help at least transiently, best results are obtained with multidisciplinary care that involves counseling and physical therapy.

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in the basal ganglia. Numerous other studies of dystonia have revealed focal lesions of the basal ganglia due to stroke, inherited metabolic defects, or other pathologies. Even when lesions are not overtly visible on structural imaging studies such as MRI or CT, abnormalities in the basal ganglia often can be found using functional imaging studies such as positron emission tomography (PET) or functional MRI (fMRI).

More recently, many studies have indicated that all forms of dystonia may not share the same anatomic pathology. Several studies have indicated that dysfunction of other regions may also cause dystonia, most notably the cerebellum.[33] Similar to the basal ganglia, both structural and functional imaging studies have pointed to the cerebellum for certain types of dystonia. Additionally, subclinical cerebellar signs occur in several types of dystonia,[34] and recognition of a large group of disorders has been growing in which dystonia and ataxia are combined.[10,35]

The modern conceptual framework is that dystonia results from dysfunction of a motor network that involves the basal ganglia, cerebellum, and cerebral cortex.[33,36] Other regions may also play a role. For example, it has been suggested that cervical dystonia results from defects in centers for head control in the midbrain.[37,38] How these networks might be affected to cause different types of dystonia remains to be determined. Dystonia could be caused by defects in one node of the network, a combination of nodes, or even abnormal communication between nodes.[34]

KEY POINTS

- More than 100 known causes for dystonia exist.
- Genetic forms of dystonia should be referred to by the name of the gene, not the DYT locus name.
- Dystonia results from dysfunction of a motor network that includes the basal ganglia, cerebellum, and sensorimotor cortex.

TREATMENT

It is not feasible to use a universal treatment algorithm for all types of dystonia because so many different subtypes exist. However, some general principles are useful. As described above, a careful diagnostic evaluation is an essential starting point because treatments are available to target the causal mechanisms for some subtypes (TABLE 5-5).[25] Other management options include counseling, physical therapy, oral medications, botulinum neurotoxin (BoNT) injections, and neurosurgical procedures.

Counseling

Counseling is an important starting place in management. Psychiatric comorbidities are common, including depression, anxiety, and social withdrawal.[9] Many patients are misdiagnosed for years, leading to frustration and mistrust of medical providers. Counseling is important for identifying any comorbidities and regaining trust.

In addition, it is important to recognize that few therapies are curative for dystonia. Most therapies are symptomatic, and the best outcomes are often achieved with an empirical trial-and-error approach, which takes time and can be frustrating. An early and frank discussion that sets realistic expectations for treatment is essential. In addition, the Useful Websites section at the end of this article lists several online resources that patients can turn to for more information.

Physical Therapy and Related Procedures

Physical therapy and related procedures seem intuitively useful when patients have excessive muscle contractions leading to soreness and abnormal postures. As a result, many patients ask about physical therapy, stretching or

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TABLE 5-5 **Inherited Dystonias With Specific Treatments Available**

Disorder	Gene	Typical Age at Onset[a]	Typical Clinical Features[b]	Treatment
Abetalipoproteinemia (Bassen-Kornzweig syndrome)	*MTTP*	Childhood to early adulthood	Progressive ataxia, chorea, dystonia (often oromandibular), seizures, acanthocytosis, retinitis pigmentosa, fat malabsorption syndrome	Early treatment with vitamin E and reduced-fat diet can prevent or reduce symptoms
Aromatic L-amino acid decarboxylase deficiency	*AADC*	Infancy	Motor delay with hypotonia and dystonia, oculogyric crises, autonomic dysfunction	Dopamine agonists and monoamine oxidase inhibitors can partly reverse symptoms in some patients
Ataxia with vitamin E deficiency	*TTPA*	Childhood to early adulthood	Ataxia, visual loss, neuropathy; occasionally patients present instead with dystonia	Early treatment with vitamin E can prevent or reduce symptoms
Biotin-thiamine–responsive basal ganglia disorder	*SLC19A3*	Childhood	Encephalopathic crisis leading to generalized dystonia	Biotin and thiamine can reverse or prevent symptoms
Biotinidase deficiency	*BTD*	Infancy	Encephalopathy with motor delay, dystonia, seizures, visual and auditory impairment, skin rash	Early treatment with biotin can prevent or reduce symptoms
Cerebral folate deficiency	*FLR1, SLC46A1*	Early childhood to adolescence	Developmental delay, ataxia, dystonia, seizures, and neuropsychiatric disturbances	Folinic acid can prevent or reduce symptoms
Cerebrotendinous xanthomatosis	*CYP27A1*	Late childhood to adulthood	Ataxia, spasticity, dementia, dystonia, myoclonus, and tendon xanthomas	Chenodeoxycholic acid may prevent progression or reverse some symptoms
Cobalamin deficiencies (inherited subtypes A through G)	Multiple	Infancy	Encephalopathy with motor delay, ataxia, spasticity, dystonia, seizures, and bone marrow abnormalities	Cobalamin derivatives or protein restriction or both can mitigate symptoms
Coenzyme Q_{10} deficiency	Multiple	Any age	Varied phenotypes of progressive ataxia or encephalopathy, sometimes with dystonia	Coenzyme Q_{10} can prevent or reduce symptoms
Cerebral creatine deficiency type 3	*GAMT, AGAT*	Infancy	Global delay, myopathy, generalized dystonia	Creatine with or without arginine restriction can mitigate symptoms
Dopa-responsive dystonia, classic	*GCH1*	Early childhood to late adulthood	Dystonia often combined with parkinsonism	Levodopa can reverse symptoms

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Disorder	Gene	Typical Age at Onset[a]	Typical Clinical Features[b]	Treatment
Dopa-responsive dystonia, complicated	*TH, PTPS, SPR*	Infancy to adolescence	Dystonia often combined with parkinsonism, oculogyric crises, and autonomic disturbances	Levodopa, 5-hydroxytryptophan, or tetrahydrobiopterin or a combination of them can completely or partly reverse symptoms
Dystonia with brain manganese accumulation	*SLC30A10, SLC39A14*	Childhood	Progressive dystonia with parkinsonism, liver disease, and polycythemia	Chelation therapy can prevent or at least partly reverse symptoms
Galactosemia	*GALT, GALK1, GALE*	Childhood to early adulthood	Ataxia and tremor, lactose intolerance, sometimes with mild dystonia	Lactose restriction can prevent or mitigate symptoms
Glucose transporter type 1 deficiency	*SLC2A1*	Childhood to adolescence	Developmental delay, seizures; sometimes paroxysmal exertional dystonia	Ketogenic diet or triheptanoin can prevent or reduce symptoms
Glutaric aciduria type 1	*GCDH*	Early childhood to early adulthood	Developmental delay with encephalopathic crisis leading to generalized dystonia	Avoiding or treating intercurrent illness with lysine restriction can prevent encephalopathic crises
Homocystinuria	*CBS*	Childhood	Neurocognitive dysfunction, myopia, ectopic lens; sometimes generalized or paroxysmal dystonia	Methionine restriction prevents most symptoms
Maple syrup urine disease	*BCKDHA, BCKDHB, DBT*	Childhood	Intermittent encephalopathy and ataxia; sometimes with focal or paroxysmal dystonia	Leucine restriction with or without thiamine can prevent or mitigate symptoms
Methylmalonic aciduria	*MUT*	Childhood	Developmental delay, renal insufficiency, pancytopenia, generalized dystonia after encephalopathic crisis	Avoiding or treating intercurrent illness with protein restriction can prevent encephalopathic crises
Molybdenum cofactor deficiency (sulfite oxidase)	*MOCS1*	Adolescence	Developmental delay with encephalopathy and seizures; rarely patients present with dystonia and parkinsonism	Cyclic pyranopterin monophosphate can prevent symptoms
Niemann-Pick disease type C	*NPC1, NPC2*	Early childhood to early adulthood	Dementia, ataxia, spasticity, seizures, supranuclear gaze palsy; sometimes with progressive generalized dystonia	*N*-butyl-deoxynojirimycin can prevent or mitigate some symptoms
Propionic aciduria	*PCCA, PCCB*	Early childhood to adolescence	Developmental delay with generalized dystonia after encephalopathic crisis	Avoiding or treating intercurrent illness with protein restriction can prevent encephalopathic crises

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Disorder	Gene	Typical Age at Onset[a]	Typical Clinical Features[b]	Treatment
Pyruvate dehydrogenase deficiency	Multiple	Infancy	Progressive generalized or paroxysmal dystonia	Thiamine, ketogenic diet, and dichloroacetate can mitigate symptoms
Rapid-onset dystonia-parkinsonism	*ATP1A3*	Early childhood to late adulthood	Psychomotor delay with bulbar or generalized dystonia after encephalopathic crisis	Avoiding or treating intercurrent illness can prevent encephalopathic crises
Wilson disease	*ATP7B*	Early childhood to late adulthood	Liver disease, Kayser-Fleischer rings, progressive dystonia, cognitive and neuropsychiatric abnormalities	Zinc or tetrathiomolybdate can prevent or reduce symptoms

[a] For most childhood-onset disorders, rarely patients may present instead in adulthood.
[b] Partial phenotypes are common.

TABLE 5-6 **Oral Medications for Dystonia**

Medication Class and Example	Indications	Typical Dosing	Common Side Effects
Anticholinergic			
Trihexyphenidyl	Any dystonia	Start with 1 mg to 2 mg each night at bedtime and increase by 1 mg to 2 mg every 2–7 days to maximum of 100 mg/d in 3–4 divided doses	Impaired mentation, dry mouth, dry eyes, constipation, urinary retention, blurry vision
Dopaminergic			
Carbidopa/levodopa	All childhood or early-adult onset dystonia	Start with a half to 1 tablet of 25 mg/100 mg and increase every 2–7 days to a maximum levodopa dose of 20 mg/kg/d in 3–4 divided doses	Nausea, orthostasis, sleep disturbance
Tetrabenazine	Tardive dystonia, oromandibular dystonia	Start with half of a 25 mg tablet and increase by half to 1 tablet every 2–7 days to maximum of 100 mg/d in 3–4 divided doses	Parkinsonism, impaired mentation, depression, drowsiness, restlessness
γ-Aminobutyric acid–mediated			
Clonazepam	Any dystonia	Start with 0.5 mg to 1.0 mg each night at bedtime and increase by 0.5 mg to 1 mg every 2–7 days to maximum of 6 mg/d in 3–4 divided doses	Impaired mentation or coordination, drowsiness, fatigue, withdrawal reactions
Baclofen	Any dystonia	Start with 5 mg to 10 mg 3 times a day and increase by 5 mg to 10 mg every 2–7 days to maximum of 40 mg 3 times a day	Impaired mentation or coordination, fatigue, nausea, dizziness, weakness, withdrawal reactions

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strengthening exercises, yoga, chiropractic therapy, and others. Although some patients seem to benefit from these procedures, the benefits are variable and often short lived. Despite the many positive outcomes described for small open trials using various strategies, the largest and most rigorous studies fail to show any consistent benefits.[39]

In the absence of evidence-based recommendations, it is reasonable to offer physical therapy or related procedures according to patient interests. Options may include stretching to limit contractures, strengthening of antagonistic muscles, and muscle relaxation techniques to reduce pain and pulling.[39] Care must be taken to find an experienced physical therapist because some exercises or manipulations may cause unnecessary pain or worsen dystonia.

KEY POINT

● All children and young adults with unexplained dystonia must have a trial of levodopa to rule out dopa-responsive dystonia.

Oral Medications

Many different oral medications are offered to patients with dystonia[40,41]; no medications are approved for the treatment of dystonia by the US Food and Drug Administration (FDA), so all uses are off-label. No medication has been subject to large-scale, double-blinded, placebo-controlled trials. Although evidence-based reviews have been published, the use of oral medications is based largely on anecdotal experience and a few small nonblinded trials, retrospective reviews, and expert consensus (TABLE 5-6).

DOPAMINE-RELATED DRUGS. Medications that stimulate or inhibit dopamine transmission may be helpful for some patients with dystonia. Levodopa is very effective in dopa-responsive dystonia, and all children and young adults with unexplained dystonia should undergo a levodopa trial (CASE 5-2).[42–44] Doses as low as half of a 25-mg/100-mg tablet of carbidopa/levodopa 2 times a day may be sufficient, although larger doses are sometimes required. For an adequate trial, the dose must be titrated to 20 mg/kg/d of levodopa for children (approximately 1000 mg/d of levodopa for an adult) divided in 3 doses a day for a month.

In addition to dopa-responsive dystonia, levodopa can be at least partially effective for several other disorders, such as dystonia that occurs in ataxia telangiectasia,[45] spinocerebellar ataxia type 3,[46] or Parkinson disease. Levodopa is not broadly useful for other types of dystonia, including the more common adult-onset isolated focal or segmental dystonias.

Depletion of dopamine stores with inhibitors of the vesicular monoamine transporter may be useful for some types of dystonia, such as tardive dystonia. Most experience comes from tetrabenazine, although newer drugs such as valbenazine and deutetrabenazine are probably equally effective with fewer side effects. Typical side effects may include parkinsonism, drowsiness, depression, anxiety, and akathisia. Dopamine receptor antagonists also are sometimes recommended for certain types of dystonia. However, this class of medications is generally discouraged because of the risk of acute dystonic reactions and tardive dystonia.

ANTICHOLINERGICS. Drugs that block muscarinic acetylcholine receptors are frequently prescribed because they seem to be at least partly effective for many different types of dystonia, regardless of cause.[47] Trihexyphenidyl is the most commonly used although others may be equally effective, including

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benztropine, biperiden, ethopropazine, orphenadrine, and procyclidine. High doses are often required (TABLE 5-6).

Although children tolerate high doses better than adults do, they may experience problems with school performance, and abnormal movements may get worse.[48,49] Dose-limiting side effects in adults include dry mouth or dry eyes, constipation, urinary retention, memory loss, confusion, depression, blurry vision, or worsening of narrow-angle glaucoma.

γ-AMINOBUTYRIC ACID–RELATED DRUGS. Baclofen is a γ-aminobutyric acid (GABA) receptor ligand that is sometimes used to manage dystonia, especially childhood-onset dystonias with coexisting spasticity. Children without spasticity and adults with focal dystonia may also benefit, but responses vary. It also can be given intrathecally via a chronically implanted minipump. Typical side effects include sedation, confusion, dizziness, and loss of muscle tone. Sudden discontinuation is associated with severe withdrawal reactions that may include delirium and seizures.

Benzodiazepines amplify GABA transmission and also are prescribed for dystonia. Examples include alprazolam, chlordiazepoxide, clonazepam, and diazepam. Typical side effects include sedation, confusion, dizziness, or depression. These drugs can be habit forming, so dose monitoring is important and sudden discontinuation should be avoided.

MUSCLE RELAXANTS AND OTHER MEDICATIONS. Many patients request "muscle relaxants" to address overactive and sore muscles. Baclofen and benzodiazepines are sometimes included in this group. Others include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and

CASE 5-2

A 34-year-old woman with a history of cerebral palsy presented to a neurology clinic to establish care. She had severe generalized dystonia affecting her trunk, neck, and all limbs. She was seriously disabled and spent much of her time in a wheelchair. Brain MRI was normal. A careful repeat history revealed worsening of her condition from the ages of 4 to 10 years, and she could not recall a trial of levodopa.

A trial of levodopa was initiated, resulting in dramatic improvement, and she was eventually able to walk independently. Genetic testing revealed a pathologic variant in the *GCH1* gene, confirming a diagnosis of dopa-responsive dystonia.

COMMENT

This case emphasizes the importance of a levodopa trial in all patients with early-onset dystonia, even those with a long-standing diagnosis of "cerebral palsy." Cerebral palsy does not typically worsen over time, and the brain MRI often shows characteristic changes due to hypoxia-ischemia. Despite many years of disability, levodopa can still produce dramatic benefits in dopa-responsive dystonia. The most common error is to conduct a levodopa trial with a very small dose. Current recommendations are to push the levodopa dose to 20 mg/kg/d before concluding the trial failed.

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orphenadrine. Many patients seem to enjoy at least partial benefits from these medications, especially those with pain from muscle spasms.

Many other drugs also have been advocated for specific forms of dystonia. Carbamazepine and related anticonvulsant medications can be remarkably effective at very low doses for dystonic spasms in paroxysmal kinesigenic dyskinesia.[50,51] Alcohol can be beneficial in the myoclonus-dystonia syndrome, but it may be habit forming and is therefore not recommended as a routine therapy. Other options sometimes recommended include amphetamines, cannabis-related products, cyproheptadine, gabapentin, lithium, nabilone, riluzole, tizanidine, and zolpidem. Responses vary considerably, and these medications are not widely used.

Botulinum Neurotoxins

BoNTs are derived from the bacterium *Clostridium botulinum*. There are seven serotypes, but only two are available as therapeutics. Type A is marketed as onabotulinumtoxinA, incobotulinumtoxinA, and abobotulinumtoxinA. Type B is available as rimabotulinumtoxinB. Many articles compare the BoNTs in terms of efficacy, side effects, and formulations. Their similarities seem more apparent than differences, so the formulation is chosen largely based on the preferences of individual clinicians. The overall utility of the BoNTs has been summarized many times, including in several systematic evidence-based reviews.[52–54]

Many resources describe their application including doses, muscle selection, and the value of localization via EMG or ultrasound.[55,56] Procedural details are not reviewed here. Instead, this section focuses on some new trends.

BoNTs can be very effective for many types of dystonia. They are the treatment of choice for focal and segmental dystonias. They can significantly reduce abnormal movements, pain, and disability. The doses and specific muscles injected must be customized according to individual needs. Benefits usually emerge after 2 to 7 days and last for an average of 3 months.[57] However, the actual duration of benefit varies widely, from 8 to 16 weeks. As a result, it is necessary to customize not only the dose and muscle pattern but also the interval between doses.[58,59] Offering a fixed interval of 12 weeks for all patients is common but not ideal.

There also has been increasing recognition of subtypes of dystonia that are more challenging to treat with BoNT than others. Of course, patients with generalized dystonia cannot have all affected muscle groups treated, but it is feasible to target the most uncomfortable areas in these patients. Patients with cervical dystonia generally respond very well, but subtypes for which good outcomes are more challenging include those with predominant anterocollis, prominent head tremor, and long-standing fixed postures.[60] Patients with blepharospasm also generally respond well, but it can be difficult to get good responses in patients who develop apraxia of eyelid opening.[61] For laryngeal dystonia, the adductor type is easier to treat than the abductor type.[62] The most challenging subtypes include hand[63] or oromandibular dystonia.[64] For these disorders, achieving the ideal balance between alleviation of dystonia and triggering of side effects can be difficult.

Side effects are generally temporary and related to spread of the BoNT to nearby sites. For cervical or oromandibular dystonia, the most common side effect is dysphagia. For blepharospasm, the most common side effects are ptosis,

KEY POINTS

- **Carbamazepine and related anticonvulsant medications may be remarkably effective at very low doses in patients with paroxysmal kinesigenic dyskinesia.**
- **When treating dystonia, it is important to customize both the dose and the interval between doses for optimal benefits with botulinum toxin.**
- **Botulinum toxins are the treatment of first choice for focal and segmental dystonias and sometimes the most discomforting aspects in generalized dystonias.**

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diplopia, and dry eyes. For laryngeal dystonia, the most common side effect is a hoarse voice.

Systemic side effects are uncommon. Some patients describe a flulike syndrome for 3 to 5 days after their treatments.[65] A recent study has raised concern for a high prevalence of antibodies to BoNT in treated patients.[66] However, the patients in this study were all actively being treated with BoNT, with typical good therapeutic responses, so the clinical significance of these antibodies remains unclear. The development of true immune-mediated functional resistance to BoNT is rare, so alternative explanations should be sought when patients do not respond, before ascribing poor outcomes to antibodies.[67,68]

Surgical Procedures

Multiple surgical options are available for the treatment of dystonia when more conservative therapies fail. Currently, the most commonly offered procedure involves neuromodulation of brain activity via deep brain stimulation. Ablative procedures involving select brain regions or peripheral targets are applied in some circumstances.

CENTRAL NERVOUS SYSTEM NEUROMODULATION. Numerous extensive reviews of neuromodulation have been published for both children and adults with different forms of dystonia.[69–71] This procedure is best applied by multidisciplinary groups with expertise in patient selection and management of complications. This section addresses practical issues of relevance to providers who may counsel or refer patients for this treatment option.

Patient selection plays an important role in surgical outcomes. From the clinical perspective, several characteristics help predict outcomes. As a general rule, patients with shorter disease duration generally do better than those with longer durations. Patients with mobile dystonia do better than those with tonic postures or fixed contractures. Patients with isolated dystonia syndromes do better than those with more complex clinical pictures that include spasticity, ataxia, or other problems. Patients of all ages may respond well, although very young patients (younger than 12 years of age) experience higher rates of surgical complications, such as hardware infection or lead migration.

The etiology of dystonia also plays an important role in predicting outcomes. Surgical outcomes are reliably good for certain subtypes and reliably poor for others. As a result, elucidating the cause for dystonia is important when considering neuromodulation. Historically, it was often asserted that isolated dystonia syndromes responded better than dystonia syndromes combined with other neurologic features. Such assertions are now considered oversimplified. For example, good outcomes are typically associated with certain inherited dystonias whether or not they are combined with other neurologic features, such as DYT1 dystonia (*TOR1A*), myoclonus-dystonia (*SGCE),* and Lubag disease (*TAF1*).[72] Other inherited dystonias respond poorly, such as rapid-onset dystonia parkinsonism (*ATP1A3*). Patients with isolated dystonia caused by *THAP1* respond more variably.

Reliably good outcomes for neuromodulation are also expected for certain acquired forms of dystonia, such as tardive dystonia due to neuroleptics. Outcomes for dystonic cerebral palsy are more variable, with some patients responding well and others not at all.[48] Populations with unpredictable responses

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should be offered surgery only by experienced centers after careful counseling, ideally as part of longer-term efforts at elucidating the reasons for variable responses.

Long-term studies of neuromodulation surgery show sustained benefits lasting many years.[73–76] Regular access to a center experienced with managing stimulator settings and complications is essential. Shortly after surgery, regular visits are needed to adjust stimulator settings because benefits are sometimes delayed for weeks or even months. After optimal settings are achieved, return visits must be expected yearly to interrogate the device and ensure proper function. Long-term complications are not uncommon. In one study, 47 patients with DYT1 dystonia were monitored by an experienced multidisciplinary team for more than 10 years. Overall, 8.5% had delayed equipment infections requiring antibiotics and sometimes removal of equipment, 8.5% had equipment malfunction requiring reoperation, and 4.3% required reoperation for electrode repositioning.[73] Close follow-up by the neuromodulation team is therefore important for identifying and managing long-term complications.

In the past few years, numerous advances have occurred in neuromodulation therapy,[70,71] including novel insights into rare forms of dystonia for which there is little prior experience with surgery and exploration of neuroanatomic targets beyond the traditional ones. There have been advances in the equipment as well, including the development of smaller impulse generators, batteries that are rechargeable or have longer lifespans, electrical contacts that can be more precisely tuned, and stimulation that can adapt to specific physiologic triggers. Some of these advances are already in use by specific neuromodulation centers.

CENTRAL NERVOUS SYSTEM ABLATION. Lesioning specific parts of the brain was commonly performed for dystonia before the widespread adoption of neuromodulation. Neuromodulation has become the favored surgical intervention because it is reversible and adjustable. However, interest in ablative procedures has increased following the emergence of nonincisional methods, such as focused ultrasound.[70,71] Although experience is still relatively limited, ablative approaches may be appropriate in some circumstances.

Permanent ablation may be offered as a palliative procedure to patients with rapidly progressive neurodegenerative disorders with severe disability, patients who are small or frail with a high risk of hardware-related complications, those who cannot manage frequent return visits because of travel issues, or those who merely do not wish to have chronically implanted hardware. Although the newer ablative procedures are sometimes promoted as superior to deep brain stimulation because they are "noninvasive," it is important to recognize that they still produce permanent brain lesions with all of the potential short-term risks and long-term side effects.

PERIPHERAL SURGERIES. Peripheral surgeries for dystonia were common in the past and are still available but are less commonly used now that neuromodulation has become more popular. Patients with cervical dystonia may undergo selective peripheral denervation when BoNT fails and other surgical options are not feasible. Success rates are similar to those for neuromodulation.[77,78] Permanent effects include sensory loss or dysesthesia in the neck, local scarring, local muscle weakness and atrophy, and dysphagia.

KEY POINTS

- **Deep brain stimulation is the most commonly offered surgical treatment for dystonia although ablative procedures may be appropriate in some cases.**
- **Selection of patients with dystonia for surgical intervention should be done by experienced multidisciplinary teams.**
- **Focused ultrasound is becoming more popular for ablative surgery in patients with dystonia although experience is still limited.**

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Patients with blepharospasm may be offered several different procedures, including removal of redundant eyelid skin, surgical shortening of the levator palpebrae, frontalis suspension, and orbicularis oculi myectomy.[79–81] Patients with laryngeal dystonia also may be offered different procedures, including modification of the nerves, muscles, or cartilaginous structure of the larynx.[82] No large-scale studies exist that document the long-term efficacy and safety of these procedures.

CONCLUSION

In the past decade, there have been enormous strides in the appreciation of the many clinical manifestations of the dystonias, how these manifestations should be classified for optimal diagnostic and therapeutic value, their underlying biological mechanisms, and how they should be treated. All types of dystonia are treatable at least symptomatically, and several have treatments that target underlying mechanisms. As our understanding of mechanisms continues to evolve, it is likely that the number of dystonic disorders with more specific treatments will continue to grow.

ACKNOWLEDGMENTS

Special appreciation goes to Laura Scorr, MD, for providing feedback on this review. Dr Jinnah has received grant support from the National Institutes of Health (NIH) and is principal investigator for the Dystonia Coalition, which receives support through NIH grant TR001456 from the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences, and previously received support through grant NS065701 from the National Institutes of Neurological Disorders and Stroke.

USEFUL WEBSITES

BENIGN ESSENTIAL BLEPHAROSPASM RESEARCH FOUNDATION
The Benign Essential Blepharospasm Research Foundation provides information on blepharospasm and Meige syndrome.
blepharospasm.org

DYSTONIA COALITION
The Dystonia Coalition has researchers and advocacy groups in the field working together to further research about dystonias.
rarediseasesnetwork.org/cms/dystonia

DYSTONIA MEDICAL RESEARCH FOUNDATION
The Dystonia Medical Research Foundation provides support to people living with all types of dystonia.
dystonia-foundation.org

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE
The dystonias information page on the National Institute of Neurological Disorders and Stroke website provides information on what research is underway for this group of disorders.
ninds.nih.gov/Disorders/All-Disorders/Dystonias-Information-Page

NATIONAL SPASMODIC DYSPHONIA ASSOCIATION
The National Spasmodic Dysphonia Association provides information related to research, awareness, and support of people living with spasmodic dystonia and other laryngeal dystonias.
dysphonia.org

NATIONAL SPASMODIC TORTICOLLIS ASSOCIATION
The National Spasmodic Torticollis Association provides information on the signs and symptoms and treatment options of cervical dystonia.
torticollis.org

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REFERENCES

1 Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28(7): 863–873. doi:10.1002/mds.25475.

2 Fung VS, Jinnah HA, Bhatia K, Vidailhet M. Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. Mov Disord 2013;28(7):889–898. doi:10.1002/mds.25549.

3 Powell AT, Bidewell JW, Walker AC. Diagnosing idiopathic dystonia: must it take so long? Aust Health Rev 1995;18(3):120–131.

4 Jog M, Chouinard S, Hobson D, et al. Causes for treatment delays in dystonia and hemifacial spasm: a Canadian survey. Can J Neurol Sci 2011; 38(5):704–711. doi:10.1017/S0317167100012270.

5 Macerollo A, Superbo M, Gigante AF, et al. Diagnostic delay in adult-onset dystonia: data from an Italian movement disorder center. J Clin Neurosci 2015;22(3):608–610. doi:10.1016/j.jocn.2014.09.014.

6 Tiderington E, Goodman EM, Rosen AR, et al. How long does it take to diagnose cervical dystonia? J Neurol Sci 2013;335(1–2):72–74. doi:10.1016/j.jns.2013.08.028.

7 Creighton FX, Hapner E, Klein A, et al. Diagnostic delays in spasmodic dysphonia: a call for clinician education. J Voice 2015;29(5):592–594. doi:10.1016/j.jvoice.2013.10.0228.

8 Patel N, Hanfelt J, Marsh L, et al. Alleviating manoeuvres (sensory tricks) in cervical dystonia. J Neurol Neurosurg Psychiatry 2014;85(8): 882–884. doi:10.1136/jnnp-2013-307316.

9 Zurowski M, McDonald W, Fox S, Marsh L. Psychiatric comorbidities in dystonia: emerging concepts. Mov Disord 2013;28(7):914–920. doi:10.1002/mds.25501.

10 Rossi M, Balint B, Millar Vernetti P, et al.Genetic dystonia-ataxia syndromes: clinical spectrum, diagnostic approach, and treatment options. Mov Disord Clin Pract 2018;5(4):373–382. doi: 10.1002/mdc3.12635.

11 van Egmond ME, Kuiper A, Eggink H, et al. Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm. J Neurol Neurosurg Psychiatry 2014; 86(7):774–781. doi:10.1136/jnnp-2014-309106.

12 Charlesworth G, Bhatia KP, Wood NW. The genetics of dystonia: new twists in an old tale. Brain 2013; 136(pt 7):2017–2037. doi:10.1093/brain/awt138.

13 Camargos S, Cardoso F. New algorithm for the diagnosis of hereditary dystonia. Arq Neuropsiquiatr 2012;70(9):715–717. doi:10.1590/S0004-282X2012000900013.

14 Bertram KL, Williams DR. Diagnosis of dystonic syndromes—a new eight-question approach. Nat Rev Neurol 2012;8(5):275–283. doi:10.1038/nrneurol.2012.39.

15 Ludlow CL, Domangue R, Sharma D, et al. Consensus-based attributes for identifying patients with spasmodic dysphonia and other voice disorders. JAMA Otolaryngol Head Neck Surg 2018;144(8):657–665. doi: 10.1001/jamaoto.2018.0644.

16 Jinnah HA, Ceballos-Picot I, Torres RJ, et al. Attenuated variants of Lesch-Nyhan disease. Brain 2010;133(pt 3):671–689. doi:10.1093/brain/awq013.

17 Jinnah HA, Visser JE, Harris JC, et al. Delineation of the motor disorder of Lesch-Nyhan disease. Brain 2006;129(pt 5):1201–1217. doi:10.1093/brain/awl056.

18 Fu R, Ceballos-Picot I, Torres RJ, et al. Genotype-phenotype correlations in neurogenetics: Lesch-Nyhan disease as a model disorder. Brain 2013;137(pt 5):1282–1303. doi: 10.1093/brain/awt202.

19 Levy A, Lange AE. Ataxia-telangiectasia: a review of movement disorders, clinical features, and genotype correlations. Mov Disord 2018;33(8): 1238–1247. doi:10.1002/mds.27319.

20 Zech M, Jech R, Wagner M, et al. Molecular diversity of combined and complex dystonia: insights from diagnostic exome sequencing. Neurogenetics 2017;18(4):195–205. doi:10.1007/s10048-017-0521-9.

21 van Egmond ME, Lugtenberg CHA, Brouwer OF, et al. A post hoc study on gene panel analysis for the diagnosis of dystonia. Mov Disord 2017;32(4): 569–575. doi:10.1002/mds.26937.

22 Lazaridis KN, Schahl KA, Cousin MA, et al. Outcome of whole exome sequencing for diagnostic odyssey cases of an individualized medicine clinic: the Mayo Clinic experience. Mayo Clin Proc 2016;91(3):297–307. doi:10.1016/j.mayocp.2015.12.018.

23 Sawyer SL, Hartley T, Dyment DA, et al. Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. Clin Genet 2016;89(3):275–284. doi:10.1111/cge.12654.

24 Johnson NE. Whole-exome sequencing in neurologic practice: reducing the diagnostic odyssey. Neurol Genet 2015;1(4):e37. doi:10.1212/NXG.0000000000000037.

25 Jinnah HA, Albanese A, Bhatia KP, et al. Treatable inherited rare movement disorders. Mov Disord 2018;33(1):21–35. doi:10.1002/mds.27140.

26 Wickremaratchi MM, Knipe MD, Sastry BS, et al. The motor phenotype of Parkinson's disease in relation to age at onset. Mov Disord 2011;26(3): 457–463. doi:10.1002/mds.23469.

27 Yoon WT. Comparison of dystonia between Parkinson's disease and atypical parkinsonism: the clinical usefulness of dystonia distribution and characteristics in the differential diagnosis of parkinsonism. Neurol Neurochir Pol 2018;52(1): 48–53. doi:10.1016/j.pjnns.2017.11.004.

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28 Schneider SA, Bhatia KP, Hardy J. Complicated recessive dystonia parkinsonism syndromes. Mov Disord 2009;24(4):490–499. doi:10.1002/mds.22314.

29 Marras C, Lang A, van de Warrenburg BP, et al. Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society Task Force. Mov Disord 2016;31(4):436–457. doi:10.1002/mds.26527.

30 Weisheit CE, Pappas SS, Dauer WT. Inherited dystonias: clinical features and molecular pathways. Handb Clin Neurol 2018;147:241–254. doi:10.1016/B978-0-444-63233-3.00016-6.

31 Balint B, Mencacci NE, Valente EM, et al. Dystonia. Nat Rev Dis Primers 2018;4(1):25. doi:10.1038/s41572-018-0023-6.

32 Quartarone A, Hallett M. Emerging concepts in the physiological basis of dystonia. Mov Disord 2013;28(7):958–967. doi:10.1002/mds.25532.

33 Neychev VK, Gross RE, Lehéricy S, et al.The functional neuroanatomy of dystonia. Neurobiol Dis 2011;42(2):185–201. doi:10.1016/j.nbd.2011.01.026.

34 Prudente CN, Hess EJ, Jinnah HA. Dystonia as a network disorder: what is the role of the cerebellum? Neuroscience 2014;260:23–35. doi:10.1016/j.neuroscience.2013.11.062.

35 Nibbeling EA, Delnooz CC, de Koning TJ, et al. Using the shared genetics of dystonia and ataxia to unravel their pathogenesis. Neurosci Biobehav Rev 2017;75:22–39. doi:10.1016/j.neubiorev.2017.01.033.

36 Jinnah HA, Neychev V, Hess EJ. The anatomical basis for dystonia: the motor network model. Tremor Other Hyperkinet Mov (N Y) 2017;7:506. doi:10.7916/D8V69X3S.

37 Shaikh AG, Zee DS, Crawford JD, Jinnah HA. Cervical dystonia: a neural integrator disorder. Brain 2017;139(pt 10):2590–2599. doi:10.1093/brain/aww141.

38 Hutchinson M, Isa T, Molloy A, et al. Cervical dystonia: a disorder of the midbrain network for covert attentional orienting. Front Neurol 2014;5:54. doi:10.3389/fneur.2014.00054.

39 Prudente CN, Zetterberg L, Bring A, et al. Systematic review of rehabilitation in focal dystonias: classification and recommendations. Mov Disord Clin Pract 2018;5(3):237–245. doi:10.1002/mdc3.12574.

40 Pirio Richardson S, Wegele AR, Skipper B, et al. Dystonia treatment: patterns of medication use in an international cohort. Neurology 2017;88(6):1–8. doi:10.1212/WNL.0000000000003596.

41 Jinnah HA, Factor S. Diagnosis and treatment of dystonia. In: Jankovic J, editor. Neurologic clinics. Elsevier, 2015:77–100. doi:10.1016/j.ncl.2014.09.002.

42 Wijemanne S, Jankovic J. Dopa-responsive dystonia–clinical and genetic heterogeneity. Nat Rev Neurol 2015;11(7):414–424. doi:10.1038/nrneurol.2015.86.

43 Lee WW, Jeon BS. Clinical spectrum of dopa-responsive dystonia and related disorders. Curr Neurol Neurosci Rep 2014;14(7):461. doi:10.1007/s11910-014-0461-9.

44 Kurian MA, Gissen P, Smith M, et al. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. Lancet Neurol 2011;10(8):721–733. doi:10.1016/S1474-4422(11)70141-7.

45 Charlesworth G, Mohire MD, Schneider SA, et al. Ataxia telangiectasia presenting as dopa-responsive cervical dystonia. Neurology 2013;81(13):1148–1151. doi:10.1212/WNL.0b013e3182a55fa2.

46 Wilder-Smith E, Tan EK, Law HY, et al. Spinocerebellar ataxia type 3 presenting as an L-DOPA responsive dystonia phenotype in a Chinese family. J Neurol Sci 2003;213(1–2):25–28. doi:10.1016/S0022-510X(03)00129-1.

47 Greene P, Shale H, Fahn S. Experience with high dosages of anticholinergic and other drugs in the treatment of torsion dystonia. Adv Neurol 1988;50:547–556.

48 Fehlings D, Brown L, Harvey A, et al. Pharmacological and neurosurgical interventions for managing dystonia in cerebral palsy: a systematic review. Dev Med Child Neurol 2018;60(4):356–366. doi:10.1111/dmcn.13652.

49 Harvey AR, Baker LB, Reddihough DS, et al. Trihexyphenidyl for dystonia in cerebral palsy. Cochrane Database Syst Rev 2018;5: CD012430. doi:10.1002/14651858.CD012430.pub2.

50 Houser MK, Soland VL, Bhatia KP, et al. Paroxysmal kinesigenic choreoathetosis: a report of 26 patients. J Neurol 1999;246(2):120–126. doi:10.1007/s004150050318.

51 Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. Ann Neurol 1995;38(4):571–579. doi:10.1002/ana.410380405.

52 Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86(19):1818–1826. doi:10.1212/WNL.0000000000002560.

53 Castelão M, Marques RE, Duarte GS, et al. Botulinum toxin type A therapy for cervical dystonia. Cochrane Database Syst Rev 2017;12:CD003633. doi:10.1002/14651858.CD003633.pub3.

54 Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon 2013;67:94–114. doi:10.1016/j.toxicon.2012.12.004.

55 Truong D, Dressler D, Hallet M, Zachary C. Manual of botulinum toxin. Cambridge: Cambridge University Press, 2009.

56 Jost W, Valerius KP. Pictorial atlas of botulinum toxin injection: dosage, localization, application. Berlin: Quintessence Publishing Company, 2008.

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57 Marsh WA, Monroe DM, Brin MF, Gallagher CJ. Systematic review and meta-analysis of the duration of clinical effect of onabotulinumtoxinA in cervical dystonia. BMC Neurol 2014;14:91. doi:10.1186/1471-2377-14-91.

58 Ojo OO, Fernandez HH. Is it time for flexibility in botulinum inter-injection intervals? Toxicon 2015; 107(pt A):72–76. doi:10.1016/j.toxicon.2015.09.037.

59 Evidente VG, Pappert EJ. Botulinum toxin therapy for cervical dystonia: the science of dosing. Tremor Other Hyperkinet Mov (N Y) 2014;4:273. doi:10.7916/D84X56BF.

60 Jinnah HA, Goodmann E, Rosen AR, et al. Botulinum toxin treatment failures in cervical dystonia: causes, management, and outcomes. J Neurol 2016;263(6):1188–1194. doi:10.1007/s00415-016-8136-x.

61 Esposito M, Fasano A, Crisci C, et al. The combined treatment with orbital and pretarsal botulinum toxin injections in the management of poorly responsive blepharospasm. Neurol Sci 2013;35(3):397–400. doi:10.1007/s10072-013-1526-2.

62 Patel AB, Bansberg SF, Adler CH, et al. The Mayo Clinic Arizona spasmodic dysphonia experience: a demographic analysis of 718 patients. Ann Otol Rhinol Laryngol 2015;124(11):859–863. doi:10.1177/0003489415588557.

63 Lungu C, Karp BI, Alter K, et al.Long-term follow-up of botulinum toxin therapy for focal hand dystonia: outcome at 10 years or more. Mov Disord 2011;26 (4):750–753. doi:10.1002/mds.23504.

64 Termsarasab P, Tanenbaum DR, Frucht SJ. The phenomenology and natural history of idiopathic lower cranial dystonia. J Clin Mov Disord 2014;1:3. doi:10.1186/2054-7072-1-3.

65 George EB, Cotton AC, Shneyder N, Jinnah HA. A strategy for managing flu-like symptoms after botulinum toxin injections. J Neurol 2018;265(8): 1932–1933. doi:10.1007/s00415-018-8934-4.

66 Albrecht P, Jansen A, Lee JI, et al.High prevalence of neutralizing antibodies after long-term botulium neurotoxin therapy. Neurology 2019;92(1) e48–e54. doi:10.1212/WNL.0000000000006688.

67 Jinnah HA, Comella CL, Perlmutter J, et al. Longitudinal studies of botulinum toxin in cervical dystonia: why do patients discontinue therapy? Toxicon 2018;147:89–95. doi:10.1016/j.toxicon.2017.09.004.

68 Ferreira JJ, Colosimo C, Bhidayasiri R, et al. Factors influencing secondary non-response to botulinum toxin type A injections in cervical dystonia. Parkinsonism Relat Disord 2015;21(2): 111–115. doi:10.1016/j.parkreldis.2014.09.034.

69 Hale AT, Monsour MA, Rolston JD, et al.Deep brain stimulation in pediatric dystonia: a systematic review [published online ahead of print November 5, 2018]. Neurosurg Rev doi:10.1007/s10143-018-1047-9.

70 Cury RG, Kalia SK, Shah BB, et al. Surgical treatment of dystonia. Expert Rev Neurother 2018;18(6):477–492. doi:10.1080/14737175.2018.1478288.

71 Krack P, Martinez-Fernandez R, Del Alamo M, Obeso JA. Current applications and limitations of surgical treatments for movement disorders. Mov Disord 2017;32(1):36–52. doi:10.1002/mds.26890.

72 Jinnah HA, Alterman R, Klein C, et al. Deep brain stimulation for dystonia: a novel perspective on the value of genetic testing. J Neural Transm (Vienna) 2017;124(4):417–430. doi:10.1007/s00702-016-1656-9.

73 Panov F, Gologorsky Y, Connors G, et al. Deep brain stimulation in DYT1 dystonia: a 10-year experience. Neurosurgery 2013;73(1):86–93; discussion 93. doi:10.1227/01.neu.0000429841.84083.c8.

74 Tagliati M, Krack P, Volkmann J, et al. Long-term management of DBS in dystonia: response to stimulation, adverse events, battery changes, and special considerations. Mov Disord 2011; 26(suppl 1):S54–S62. doi:10.1002/mds.23535.

75 Volkmann J, Wolters A, Kupsch A, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol 2012;11(12):1029–1038. doi:10.1016/S1474-4422(12)70257-0.

76 Reese R, Gruber D, Schoenecker T, et al.Long-term clinical outcome in Meige syndrome treated with internal pallidum deep brain stimulation. Mov Disord 2011;26(4):691–698. doi:10.1002/mds.23549.

77 Contarino MF, Van Den Munckhof P, Tijssen MA, et al. Selective peripheral denervation: comparison with pallidal stimulation and literature review. J Neurol 2014;261:300–308. doi:10.1007/s00415-013-7188-4.

78 Ravindran K, Ganesh Kumar N, Englot DJ, et al. Deep brain stimulation versus peripheral denervation for cervical dystonia: a systematic review and meta-analysis. World Neurosurg 2018; pii: S1878-8750(18)32485-9. doi:10.1016/j.wneu.2018.10.178.

79 Georgescu D, Vagefi MR, McMullan TF, et al. Upper eyelid myectomy in blepharospasm with associated apraxia of lid opening. Am J Ophthalmol 2008;145(3):541–547. doi:10.1016/j.ajo.2007.10.017.

80 Grivet D, Robert PY, Thuret G, et al. Assessment of blepharospasm surgery using an improved disability scale: study of 138 patients. Ophthalmic Plast Reconstr Surg 2005;21(3):230–234. doi:10.1097/01.IOP.0000162429.97307.4D.

81 Pariseau B, Worley MW, Anderson RL. Myectomy for blepharospasm 2013. Curr Opin Ophthalmol 2013;24(5):488–493. doi:10.1097/ICU.0b013e3283645aee.

82 Ludlow CL. Treatment for spasmodic dysphonia: limitations of current approaches. Curr Opin Otolaryngol Head Neck Surg 2009;17(3):160–165. doi:10.1097/MOO.0b013e32832aef6f.

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DISCLOSURE

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Beat Dystonia, the Benign Essential Blepharospasm Research Foundation, Cure Dystonia Now, Dystonia Europe, Dystonia Inc, Dystonia Ireland, the Dystonia Medical Research Foundation, the Foundation for Dystonia Research, the National Spasmodic Dysphonia Association, and the National Spasmodic Torticollis Association).

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Jinnah discusses the unlabeled/investigational use of alprazolam, amphetamines, baclofen, benzodiazepines, benztropine, biperiden, botulinum neurotoxins, carbamazepine, carbidopa/levodopa, carisoprodol, chlordiazepoxide, chlorzoxazone, clonazepam, cyclobenzaprine, cyproheptadine, diazepam, ethopropazine, gabapentin, lithium, metaxalone, methocarbamol, nabilone orphenadrine, procyclidine, riluzole, tizanidine, trihexyphenidyl, and zolpidem for the treatment of dystonia. Dr Jinnah discusses the unlabeled/investigational use of thiamine for the treatment of biotin-thiamine–responsive basal ganglia disorder; folinic acid for the treatment of cerebral folate deficiency; chenodeoxycholic acid for the treatment of cerebrotendinous xanthomatosis; 5-hydroxytryptophan and tetrahydrobiopterin for the treatment of dopa-responsive dystonia; cyclic pyranopterin monophosphate for the treatment of molybdenum cofactor deficiency; *N*-butyl-deoxynojirimycin for the treatment of Niemann-Pick disease type C; tetrabenazine for the treatment of oromandibular dystonia; and deutetrabenazine, tetrabenazine, and valbenazine and for the treatment of tardive dystonia.

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