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Diagnosis & Treatment of Dystonia

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Synopsis

The dystonias are a group of disorders characterized by excessive involuntary muscle contractions leading to abnormal postures and/or repetitive movements. There are many different clinical manifestations and many different causes. A careful assessment of the clinical manifestations is helpful for identifying syndromic patterns that focus diagnostic testing on potential causes. If a cause can be identified, specific etiology-based treatments may be available. However, in the majority of cases, a specific cause cannot be identified, and treatments are based on symptoms. Treatment options include counseling and education, oral medications, botulinum toxin injections, and several surgical procedures. A substantial reduction in symptoms and improved quality of life can be achieved in the majority of patients by combining these various options.

Keywords

blepharospasm; botulinum toxin; cervical dystonia; deep brain stimulation; focal hand dystonia; Meige syndrome; oromandibular dystonia; spasmodic dysphonia; torticollis

Introduction

The dystonias are a group of disorders defined by specific types of abnormal movements. The essential feature is over-activity of muscles needed for movement. This over-activity can be expressed as excessive force in the primary muscles used for a movement, overflow activation of additional muscles that are not required for a movement, or co-activation of muscles that antagonize the primary muscles. The clinical expression of dystonia is determined by the severity and distribution of muscles involved. In mild cases dystonic movements appear merely as exaggerations of specific actions. In moderate cases the movements are more clearly abnormal with a quality that is cramped, stiff or twisting. In more severe cases dystonic movements appear as persistent odd postures or fixed deformities.

Dystonic movements are often slow, but they sometimes may be rapid or jerky.[1,2] Sometimes the movements may resemble tremor.[3–5] They tend to be patterned or

stereotyped in individual cases. A recent consensus work group provided the following formal definition for the dystonias:[6]

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

Virtually any region of the body may be affected, alone or in various combinations. The dystonias may emerge at any age; and once they begin, they rarely remit. Some remain relatively static, while others are progressive or intermittent. Dystonia may occur in isolation, or it may be combined with other clinical problems. The many different clinical manifestations are classified according to four dimensions (Table 1) including the region of the body affected, the age at onset, temporal aspects, and whether there are associated clinical problems.[6] Each of these dimensions has implications for diagnosis and treatment.

In addition to the widely varying clinical manifestations of the dystonias, there also are many different causes.[7] Some dystonias are inherited, others are acquired (Table 2). Some dystonias have no apparent pathology in the nervous system, while others are associated with defects that can be detected by neuroimaging or post-mortem histopathological studies. At the molecular level, multiple genes have been discovered for rare subtypes of dystonia,[8,9] and they are involved in diverse biochemical processes.[9–11] At the anatomical level, several brain regions have been implicated, leading to the concept that dystonia does not arise from dysfunction of a single brain region, but rather from dysfunction of a motor network.[12–14] Physiologically, many forms of dystonia have evidence for impaired inhibitory processes in the nervous system, abnormal sensory feedback, and/or maladaptive neural plasticity.[15–17] Determining how these diverse processes relate to one another to produce the motor syndrome we know as dystonia is a major current focus of research.[11,18]

Diagnosis

Because there are so many different clinical manifestations and causes, there are no simple algorithms for diagnosis that address all dystonias. A shotgun approach in which all possible disorders are evaluated in a “dystonia test battery” is not recommended. Available genetic test batteries are very expensive, they include only a small fraction of known causes, and the probability of finding a positive result in sporadic cases with dystonia is <1%. Another strategy sometimes recommended follows a “red flag” approach in which diagnostic testing is guided by the identification of telltale clinical features, such as a corneal Kayser-Fleischer ring or liver disease in Wilson’s disease.[19,20] This strategy is not ideal because most dystonic disorders lack red flags. Another strategy sometimes recommended is to test only for disorders where there are specific treatments that target underlying etiologies, such as Wilson’s disease where copper-lowering therapies are life saving. This strategy also is untenable, because recent progress in dystonia research has led to a long list of treatable disorders that grows every year (Table 3).

A more methodical strategy for diagnosis is shown in Figure 1. Once a diagnosis of dystonia is suspected based on clinical phenomenology, the first step is to rule out disorders that may mimic dystonia (pseudodystonia), such as those due to orthopedic, neuromuscular or psychogenic processes. The next step is to delineate the clinical syndrome according to the four dimensions used for clinical classification (Table 1). A careful delineation of the syndromic pattern, along with neuroimaging characteristics, is important because it aids in narrowing down the long list of potential etiologies for more targeted diagnostic testing.[7]

For patients with isolated dystonia, the laboratory workup depends on the age at onset, the body distribution, and whether there are affected family members. In adults with focal or segmental dystonia only, no diagnostic tests are required because they usually are unrevealing.[18,21] In adults with hemidystonia or generalized dystonia, neuroimaging is useful because the likelihood of disclosing a structural cause is higher. In sporadic adult-onset isolated dystonias, the chance of finding a genetic cause is less than 1–2%, so genetic testing usually is not cost effective, unless there are other affected family members. The diagnostic approach in younger individuals with isolated dystonia is quite different, because there is a much higher likelihood of disclosing a cause.[7] Neuroimaging is important for all early-onset cases, regardless of body distribution. Genetic testing for early-onset isolated dystonias should target the *TOR1A* gene for DYT1 dystonia and the *THAP1* gene for DYT6 dystonia.

For all patients where dystonia is combined with other neurological or systemic features, some additional workup is warranted, regardless of the age at onset or body distribution. The laboratory workup depends on the nature of the associated features and the age at onset. A recent review summarized more than 100 different disorders where dystonia may be combined with other features, organized in 18 tables according to the associated clinical features and age at onset.[7] Neuroimaging is useful in virtually all combined dystonias, because it can provide important diagnostic clues. Genetic testing for DYT1 and DYT6 dystonia is not useful in combined dystonia syndromes. Instead, laboratory testing is driven by the syndromic pattern. For example, dystonia combined with Parkinsonism leads to a relatively small list of disorders for more targeted diagnostic testing.[22–24]

When a specific etiology cannot be determined, it is important to follow patients and revise the diagnosis as additional clinical features are recognized. Many combined dystonic disorders may present first with what appears to be isolated dystonia, and additional clinical features may develop over the following months or years. One of the most common examples is idiopathic Parkinson’s disease and related Parkinsonian syndromes, where 10–15% of patients may present first with isolated dystonia of an arm or leg.[25–30] It is not until other clinical features emerge that the diagnosis becomes more obvious.

Treatment

There are many different treatment options that involve counseling and education, oral medications, intramuscular injection of botulinum neurotoxins (BoNT), physical and occupational therapy, and neurosurgical interventions. In the next section these options are

summarized individually. Subsequently, some suggestions are offered for how these individual ingredients can be combined for the best outcomes in different types of dystonia.

Education and counseling

Education and counseling are important for several reasons. Patients frequently are misdiagnosed for many years, and many are told they suffering from a psychiatric problem. Even for the most common and readily diagnosed subtypes of dystonia such as cervical dystonia, the mean time from onset of symptoms to diagnosis is 4–6 years.[31–33] These delays in reaching a diagnosis often lead to frustration and mistrust of medical providers. Education and counseling are important for regaining trust so that patients are more likely to accept recommendations.

Education and counseling also are important because few therapies are curative. Achieving the best outcome often requires an empirical trial and error approach, which can sometimes amplify existing frustration and mistrust. A frank discussion of treatment options is essential to ensure that expectations are realistic. It is also worth bearing in mind that there is a high rate of psychiatric co-morbidity in the dystonias including depression, anxiety and social withdrawal.[34–37] An open discussion of how these factors may influence overall quality of life is important.

Finally, many patients learn about their medical diagnoses and treatment options via the internet, which is not always a reliable source of information. Educating patients about the most reliable online sources of information can help to avoid misunderstandings. Table 4 provides a summary of some internet sites where information is regularly updated, and other educational and research opportunities are available to patients. Most of these groups also provide informational brochures, newsletters and local patient support group meetings where patients can obtain new information.

Physical & Occupational Therapy

Patients frequently ask about the value of exercise and physical therapy, because they seem intuitively helpful for addressing abnormal muscle activity and pain. Although many patients seem to appreciate physical therapy, benefits often are temporary, and there are no large-scale double-blind studies that demonstrate objective benefits to justify regular application.

Several investigators have sought to demonstrate objective improvements using specific methods based on theories regarding the pathophysiology of dystonia. For example, the theory that dystonia results from maladaptive neural plasticity[15,38,39] has led to attempts to re-train normal patterns of activity via “constraint-induced” movement training to limit abnormal movements while reinforcing normal ones,[40,41] “sensorimotor retuning” with intensive exercises,[42] “slow down” therapy,[43] active exercise,[44] and EMG-biofeedback.[45,46] Theories regarding maladaptive plasticity also have led to the opposing strategy of attempting to erase abnormal plasticity via lengthy periods of immobilization.[47] Theories relating the pathophysiology of dystonia to defects in sensory processes or sensorimotor integration[48] have led to attempts to alter sensory feedback as a treatment strategy. Various methods have been exploited including modification of sensory inputs,[49,50] “kinesogenic

taping,"[51] transcutaneous electrical nerve stimulation,[52] and augmentation of somatosensory discrimination by Braille training.[53]

Despite the enthusiasm for physical therapy in dystonia, systematic reviews have concluded that there is insufficient evidence to recommend any particular strategy.[45,46] There are several reasons for the lack of clear guidelines. First, most of the studies have been quite small with outcomes that often were not reproducible, and the larger studies frequently demonstrated wide response variations among patients. Second, the reported benefits often have been quite small, transient, or subjective. The modest benefits of individual techniques have led to attempts to combine treatments using "multimodal" strategies, further obscuring the value of specific interventions. Third, there is a tradition in physical therapy to customize procedures according to the needs of individual patients. As a result, large studies using uniform protocols are scarce. Double-blind and placebo-controlled studies are rare also in part because of the difficulty in designing an appropriate control group to rule out non-specific placebo effects. Finally, many of the methods are cumbersome and time consuming, limiting enthusiasm for clinical application.

Enthusiasm for specific strategies also is blunted by concerns that some well-intentioned designs may be harmful. For example, significant improvements have been reported for patients with hand dystonia following 4–6 weeks of immobilization with a rigid splint.[54,55] However, broad adoption has been limited by the long duration of splinting, side effects of hand clumsiness and weakness following splinting, and concerns that prolonged immobilization can trigger more severe fixed dystonia, sometimes as part of the complex regional pain syndrome.[56] Similarly, transcutaneous electrical nerve stimulation has been reported to be helpful in some patients,[52] yet detrimental to others.[57] Despite these limitations, the available studies have provided some promising suggestions that deserve further exploration and development before more general recommendations can be formulated.[58]

In the absence of solid evidence to guide more specific recommendations, it seems reasonable to incorporate general physical therapy methods according to patient preferences. These may include regular stretching exercises to mitigate against contractures, muscle relaxation methods to attenuate pulling and pain, and strengthening of antagonist muscles to balance abnormal postures. Various assistive devices also are available to allow more significantly disabled patients to function more independently.

Oral medications

There are multiple articles summarizing oral medications for dystonia,[59–63] including two systematic evidence-based reviews.[64,65] None of the commonly used drugs has been subject to large-scale, double-blinded, placebo-controlled trials. None of them has been FDA approved for treatment of dystonia. Much of the evidence supporting the use of these drugs comes from small controlled trials, non-blinded trials, retrospective reviews, and anecdotal experience (Table 5).

Acetylcholine-related drugs—One of the most frequently prescribed classes of medications for the dystonias include anticholinergics such as trihexyphenidyl, benztropine,

biperidin, ethopropazine, orphenadrine, and procyclidine. These drugs are thought to work by blocking muscarinic acetylcholine receptors in the basal ganglia.[66] Their use is supported by multiple retrospective studies,[67] and one prospective, double-blind trial of trihexyphenidyl that showed clinically significant improvements in 71% of patients on an mean dose of 30 mg daily.[68] However this study included only 31 patients with predominantly isolated dystonia, and a mean age of 19 years. Similar studies of children with dystonia associated with cerebral palsy showed that a significant proportion may worsen with anticholinergics.[69] There are no prospective double-blind, placebo-controlled trials of anticholinergics for older adults, who are less likely to tolerate their many side effects.[70,71]

Despite the limited and sometimes conflicting information, anticholinergics remain in broad use because they seem to be at least partly effective for many types of dystonia, regardless of the underlying etiology. Trihexyphenidyl must be started at a low dose, for example 2 mg twice daily. It can be increased by 2 mg every few days until benefits are observed or side effects emerge. Effective doses range from 6–40 mg daily, divided across 3–4 doses. Typical side effects include memory loss, confusion, restlessness, depression, dry mouth, constipation, urinary retention, blurry vision or worsening of narrow-angle glaucoma

Dopamine-related drugs—Medications that augment or suppress dopaminergic transmission in the basal ganglia may be extraordinarily helpful in select populations of patients with dystonia. Augmenting dopamine transmission with levodopa is dramatically effective in dopa-responsive dystonia, which is most often caused by mutations in the *GCH1* gene encoding the enzyme GTP-cyclohydrolase. [72,73] Many patients respond to doses as low as half of a 25/100 mg tablet of carbidopa/levodopa twice daily, although others require larger doses.[72] For an adequate trial of levodopa, the dose should be increased slowly to 1000 mg in an adult (or 20 mg/kg for children) divided across three daily doses for one month before concluding it will not be effective. In addition to levodopa, patients with classical dopa-responsive dystonia respond to dopamine agonists and drugs that block dopamine metabolism such as monoamine oxidase inhibitors.

Levodopa is also at least partially effective in other disorders affecting dopamine synthesis that are caused by deficiency of tyrosine hydroxylase, sepiapterin reductase, and others.[74] It may also be effective in some other rare disorders such as the dystonia in some cases of spinocerebellar ataxia type 3[75] or variant forms of ataxia telangiectasia,[76] and for dystonia in Parkinson's disease. Aside from these specific populations, levodopa and dopamine agonists are not broadly useful for other types of dystonia, such as the more common adult-onset isolated focal or segmental dystonias.[77]

Medications that suppress dopaminergic transmission also may be useful for specific subgroups of patients. Although dopamine receptor antagonists have been used with variable success in small un-blinded studies, their use is generally discouraged because the risk for development of acute dystonic reactions and tardive syndromes may lead to diagnostic confusion. However, depletion of dopamine with tetrabenazine does not carry these same risks, and it may be useful for some patients with dystonia, particularly those with tardive dystonia.[78–80] It can be started at half of a 25 mg daily daily, and titrated up by a half tablet

every 3–5 days, to a target of 25–100 mg daily. Dose-limiting side effects include drowsiness, parkinsonism, depression, insomnia, nervousness, anxiety, and akathisia.

GABA-related drugs—Another frequently prescribed group of medications is the benzodiazepines such as alprazolam, chlordiazepoxide, clonazepam, and diazepam. They are thought to work by amplifying transmission through GABA receptors. There are no large double-blind and controlled studies of the benzodiazepines in dystonia. Their use is supported by multiple small or retrospective studies. Anecdotal experience suggests they may be most useful for suppressing phasic aspects of dystonia, such as blinking in blepharospasm or tremor-dominant forms of dystonia.[67,81,82] They also appear to be useful in the paroxysmal dyskinesias, where dystonia can be a prominent feature.[83] Common side effects include sedation, impaired mentation and coordination, and depression. There also is a risk for tachyphylaxis and dependency, so abrupt discontinuation or sudden large decreases in doses should be avoided.

Baclofen is a GABA receptor agonist that also is often used in dystonia. There are no controlled studies to guide recommendations for its use, but several retrospective studies and anecdotal reports suggest it is mot often useful in childhood-onset dystonias, especially those with co-existing spasticity of the lower limbs.[67,84] Some adults also may benefit, but most do not. Effective oral doses range from 30–120 mg daily divided across 3–4 doses. Common side effects include sedation, nausea, impaired mentation, dizziness and loss of muscle tone. Abrupt discontinuation or sudden large decreases in doses can be associated with withdrawal reactions that include delirium and seizures.

Baclofen also can be delivered intrathecally via chronically implanted minipumps, where it may be useful in a subpopulation of patients with dystonia.[85–87] Here again, it has been most often employed in children where dystonia is combined with spasticity, especially in the lower limbs. The side effects are similar to those listed above for oral administration, with additional complications related to the implanted device. These complications include pump malfunction, catheter obstruction or leaks, or infection of the equipment.

Muscle relaxants—Many patients request “muscle relaxants” because they seem intuitively useful for overactive and sore muscles. This is a broad category of medications with diverse mechanisms of action that include baclofen and benzodiazepines described above, along with carisoprodol, chlorzoxazone, cyclobenzeprine, metaxalone, methocarbamol, and orphenadrine. There are no formal studies to guide recommendations for the use of these drugs in dystonia, and responses vary widely. Nevertheless, many patients derive at least partial benefits, especially those with pain from uncontrolled muscle pulling.

Other medications—A wide variety of other drugs have been advocated for specific forms of dystonia, generally based on small and non-blinded studies or anecdotal experiences. For example, carbamazepine and other anticonvulsants seem particularly useful for dystonic spasms in paroxysmal kinesigenic dyskinesia,[88–90] and alcohol is useful in the myoclonus-dystonia syndrome.[91] Mexiletine and intravenous lidocaine may be helpful in some cases.[92,93] Other options suggested for specific populations include amphetamines,

cannabidiol, cyproheptidine, gabapentin, lithium, nabilone, riluzole, tizanidine, and zolpidem.

Botulinum Neurotoxins

Medical BoNTs are derived from a neurotoxic protein produced by the bacterium *Clostridium botulinum*. The bacterial toxin causes a paralytic disorder known as botulism, but medical grade BoNT is purified and attenuated so that local intramuscular injections suppress overactive muscles in dystonia. There are seven distinct serotypes, A-G. Type A is marketed as onabotulinumtoxinA (Botox™), abobotulinumtoxinA (Dysport™), and incobotulinumtoxinA (Xeomin™). Type B is marketed as rimabotulinumtoxinB (Myobloc™). Their safety and efficacy have been the subject of multiple prior summaries, including several systematic evidence based reviews.[64,94,95] They are very effective for many types of dystonia, significantly reducing abnormal movements and associated disability, and improving overall quality of life.

Many detailed resources are available for application of the BoNTs including target muscle selection, dosing, and the use of ancillary procedures for localization such as electromyography and ultrasound.[96,97] The technical details associated with administration of BoNTs will not be reviewed here. Instead, the focus is on practical issues faced by physicians who may refer patients for BoNT treatments, and on some of the most common questions regarding their application. The first important issue involves the type of dystonia. The botulinum neurotoxins (BoNTs) are considered the treatment of first choice for most focal and segmental dystonias including blepharospasm, cervical dystonia, oromandibular and laryngeal dystonias, limb dystonias, and others. The benefits from injections usually emerge after 2–7 days, and they last for approximately 3–4 months.[98] Most patients return for treatments 3–4 times yearly. BoNTs also can be valuable for patients with broader patterns of dystonia, where they are often under-utilized. For these patients, the goal is to target the regions that cause the most discomfort. For example, patients with dyskinetic cerebral palsy often have generalized dystonia with prominent involvement of the neck, and treatment with BoNT can alleviate this discomfort ant reduce the risk of acquired myelopathy.[99]

The BoNTs are dramatically effective for most focal dystonias, but it can be challenging to get good results with certain subtypes. Some patients with blepharospasm have co-existing apraxia of eyelid opening, which is more difficult to treat with BoNT.[100] Injections into the pretarsal portion of the orbicularis oculi muscles may improve outcomes in these cases.[101,102] Among patients with cervical dystonia, those with prominent anterocollis can be more difficult to treat.[103] Deep injections into pre-vertebral muscles have been advocated,[104,105] although responses vary. For laryngeal dystonias, spasmodic adductor dysphonia responds more predictably than spasmodic abductor dysphonia.[106,107] Oromandibular and lingual dystonias can sometimes be challenging to treat, although good outcomes can be achieved in experienced hands.[108–112] Because there are so many small muscles that work together for coordinated activities, it can be difficult to achieve satisfactory outcomes for hand dystonias. Some patients enjoy dramatic benefits with very

small doses, but achieving the right dose to avoid weakness or involvement of nearby muscles can be difficult to balance.[113]

Another important issue involves side effects. There are no deleterious long-term side effects even after decades of treatment, apart from a small risk of developing resistance due to antibodies that neutralize the BoNT protein. However, the development of immunologically mediated resistance is rare with current preparations of BoNT.[114,115] The short-term side effects depend mostly on local diffusion from the sites of injection. For blepharospasm the most common side effects are ptosis, local hematoma formation, tearing, and rarely blurry vision or diplopia. For cervical dystonia the most common side effects are dysphagia, excessive neck muscle weakness, and occasionally dry mouth. For laryngeal dystonias the most common side effects are hoarsenss or hypophonia, and rarely dysphagia and aspiration. For limb dystonias the most common side effects involve excessive weakening, or weakness of nearby muscles. Systemic side effects are unusual, but a few patients complain of a flu-like syndrome for 3–5 days after their treatments.

A third issue involves the selection of a specific product. Many articles have summarized differences among the BoNTs regarding efficacy, side effects, and formulations. However, there are few scientifically rigorous comparisons, and the similarities are more striking than the differences (Table 6). The choice of product depends largely on the experience and preferences of individual providers.

Surgical Interventions

Multiple surgical interventions are available for the treatment of the dystonias. Typically these more invasive approaches are reserved for patients who fail more conservative therapies. The most common intervention involves neuromodulation of brain activity via an implanted electrical impulse generator, although focal ablation of select brain areas and peripheral approaches that target nerves or muscles can be applied in some circumstances.

Neuromodulation—Neuromodulation is synonomous with deep brain stimulation (DBS). The term neuromodulation is increasingly preferred because some targets may not be “deep” and “stimulation” implies a mechanism that has not been established. Several extensive reviews on neuromodulation have been published recently,[116–118] including a whole issue of the journal *Movement Disorders* (volume 26, supplement 1, 2011). Here, the focus is on practical issues of relevance to any physician who may council patients regarding these options. The issues include patient selection for best outcomes, long-term expectations, and some ongoing debates.

Some patients with dystonia respond quite well to neuromodulation, while others derive no benefit. Many years of experience have provided some important insights into several factors that predict responses.[118,119] Patients with isolated generalized dystonia syndromes (previously “primary” dystonia) tend to respond most consistently, with the most objective blinded studies showing improvements in standardized dystonia rating scales of 40–60%.[120,121] Among this patient population best outcomes appear to be associated with younger ages, shorter disease durations, and those who have the common *TOR1A* mutation for DYT1 dystonia. There is insufficient evidence to predict outcomes in the more recently

discovered genes including the *THAP1* gene for DYT6. Patients with fixed contractures or scoliosis do not do so well as those with more a more mobile syndrome.

Patients with isolated focal and segmental dystonias also appear to respond well to neuromodulation, although perhaps less predictably than those with isolated generalized dystonia. This group includes patients with relatively localized or segmental patterns involving the neck, face, trunk or limbs. Patients with dystonic syndromes that are combined with other neurological features (previously “dystonia plus” or “secondary” dystonias) respond variably. Some subtypes consistently respond very well, for example myoclonus dystonia and tardive dystonia. Others have a consistently poor outcome (e.g. degenerative disorders) or are less predictable (e.g. cerebral palsy). One of the reasons for the poor outcomes in some populations is that it is difficult to detect a stable benefit for progressive degenerative disorders, or for disorders where dystonia is combined with other motor defects such as spasticity that are not expected to improve with neuromodulation. These populations should be considered for surgery only by very experienced centers after careful counseling, ideally as part of a methodical study aimed at elucidating risk/benefit profiles.

The long-term outcomes of neuromodulation are good,[122–124] with benefits sustained for many years, and some studies reporting good outcomes even after 10 years.[125] Ongoing access to an experienced center to adjust stimulator settings and address potential complications is essential. Benefits from surgery can be delayed for weeks or even months, requiring frequent visits to adjust stimulator settings for optimal outcomes. Return visits also should be anticipated every 2–4 years for battery replacement. In one study of 47 cases with DYT1 dystonia followed by a very experienced multidisciplinary neuromodulation center for more than 10 years, 8.5% had delayed post-operative infection of equipment requiring antibiotics and/or equipment removal, 8.5% had malfunction of equipment such as impulse generator failure or lead defects, and 4.3% required revisions of lead location.[125] These observations indicate that close follow-up by an experienced team is essential for long-term maintenance therapy. This requirement for return visits presents a barrier for some patients who may live far from experienced providers.

There are several unresolved questions that the counseling physician may be asked to address. One is the ideal surgical target.[116,118] The internal segment of the globus pallidus (GPi) is the traditional target used by most centers. However, observations that patients with dystonia sometimes develop bradykinesia in unaffected body regions or gait failure have led to interest in other targets such as the subthalamic nucleus. On the other hand, neuromodulation of the subthalamic nucleus has been associated with dyskinesias, weight gain, and psychiatric changes. Others have targeted various regions of the thalamus, usually for focal hand dystonia and those with prominent tremor.[126–128] The “ideal” target remains unknown. Whether this target varies according to the subtype of dystonia also remains uncertain. As a result the selection of targets often is driven by the opinions of individual centers.

Another unresolved question involves the expected outcomes for patients with dystonias combined with other neurological features (previously “secondary” dystonias). Aside from tardive dystonia and myoclonus dystonia, there is insufficient information to counsel

interested patients regarding expectations. The lack of information should not be viewed as an absolute contraindication for surgery, but patients must be clearly informed about the chances for failure.

Ablative approaches—Making controlled focal lesions in specific parts of the brain was the most common surgical procedure conducted for dystonia patients before neuromodulation became more popular.[129] Lesions were made in a variety of locations, most notably the thalamus, globus pallidus and cerebellum. Neuromodulation rapidly became more popular because it is more readily tunable, and because it is reversible in the event that intolerable side effects develop. However, neuromodulation has its own risk of complications related to the hardware, and it is expensive. Therefore, there is still a role for ablative procedures in some circumstances.[116,129]

Ablative procedures may be useful in developing countries where the cost of equipment for neuromodulation and requirements for regular follow-up are prohibitive. Ablations are also useful for patients with a body habitus that presents a high risk for hardware-related complications, such as those with severe dystonia and fixed contractions, or very young or otherwise small patients. They may be offered to patients who suffer repeated hardware infections, or merely do not wish to have chronically implanted hardware. They may also be appropriate as palliative procedures for patients with severe illness who cannot tolerate surgery to install and maintain the hardware, and for some progressive neurodegenerative disorders.

Peripheral surgeries—Another category of surgeries often offered to patients with dystonia before BoNTs and neuromodulation became more popular involved directly sectioning or destroying overactive muscles or the nerves controlling them. These procedures are far less commonly used today, but they are still offered by some centers. They are covered briefly here for physicians encountering patients who may ask about them.

Selective peripheral denervation may be offered to patients with cervical dystonia who fail oral agents and botulinum toxins. The procedure involves extra-spinal sectioning of nerves to specific muscles, so best outcomes are seen for patients with a limited number of muscles involved (e.g. pure torticollis or pure laterocollis). Success rates are reported from 60–90%.[130–135] Side effects may include permanent somatosensory loss or dysesthesia in an isolated region of the neck, cosmetic changes associated with scaring or muscle atrophy, muscles weakness, and dysphagia. Abnormal movements may re-emerge after several weeks or years, a phenomenon that may reflect re-innervation or progression of the underlying disorder.

A variety of procedures are offered to patients with blepharospasm too. They include orbicularis myectomy, frontalis suspension, surgical shortening of the levator palpebrae, and removal of redundant eyelid skin.[136–138] None of these procedures has been subject to rigorous trials, so they usually are offered only to patients who fail botulinum toxins. Included are patients who are resistant to the toxins, and those with co-existing apraxia of eyelid opening that may respond poorly to the toxins.

There also are several procedures in use for patients with laryngeal dystonia.[139,140] Patients with spasmodic dysphonia may undergo thyroplasty to modify the cartilaginous structure of the larynx or thyro-aretynoid myectomy. The most common approach involves sectioning the recurrent laryngeal nerve to the thyro-arytenoid and annealing the stump to the ansa cervicalis. Complications can include transient or permanent voice impediment, dysphagia, and return of symptoms requiring re-operation.

Strategies for Combining Therapies for Specific Populations

Because there are so many different clinical manifestations and causes of the dystonias, it is not feasible to devise a universal treatment algorithm for all subtypes that combines the various medical and surgical options outlined above. Although treatment plans must be individualized, there are some useful guiding principles. The first step is to delineate the diagnosis (Figure 1). The diagnostic subtype is important for the application of some types of treatments that target underlying etiological mechanisms and substantially modify the course of the disease (Table 3). The next step involves counseling to address expectations from treatment and any psychiatric comorbidities.

For the majority of patients where disease-modifying therapies are not yet available, treatments are symptomatic. For late-onset focal or segmental dystonia, BoNTs are the treatment of first choice. Because symptoms may wax and wane in severity, an oral agent may be offered as adjunctive therapy to use when needed. When BoNTs and oral medications are not adequate, patients with focal and segmental dystonias may undergo more invasive surgical approaches.

For adults with generalized dystonia and all early-onset dystonias regardless of body distribution where diagnostic testing does not reveal a cause with etiology-based treatments, a trial of levodopa is mandatory to address the possibility of dopa-responsive dystonia. There are no data to guide the exact age cut-off where a levodopa trial is essential, but many providers proceed with a levodopa trial for any patient with isolated dystonia who is <40 years old. Following this trial, other oral agents may also be attempted. BoNT may be offered to those where one particular region of the body creates the most disability, and surgical interventions are offered when oral agents and BoNT provide insufficient benefits.

Conclusions

The treatment of patients with dystonia has improved dramatically over recent years. There is a rapidly growing list of specific subtypes with specific treatments that target the underlying etiology. This list is expected to continue to grow, as more is learned about the underlying causes for dystonia. There are four widely available BoNTs preparations. They are highly effective in the treatment of focal and segmental dystonias, and can be of benefit in patients with broader distributions too. Neuromodulation of the brain and peripheral surgeries that target nerve or muscles can also be very useful when more conservative methods fail. Knowing how to mix and match these various treatment modalities for specific populations can be challenging, but significant benefits can be achieved in the vast majority of patients.

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Abbreviations & acronyms

BoNT	botulinum neurotoxin
DBS	deep brain stimulation

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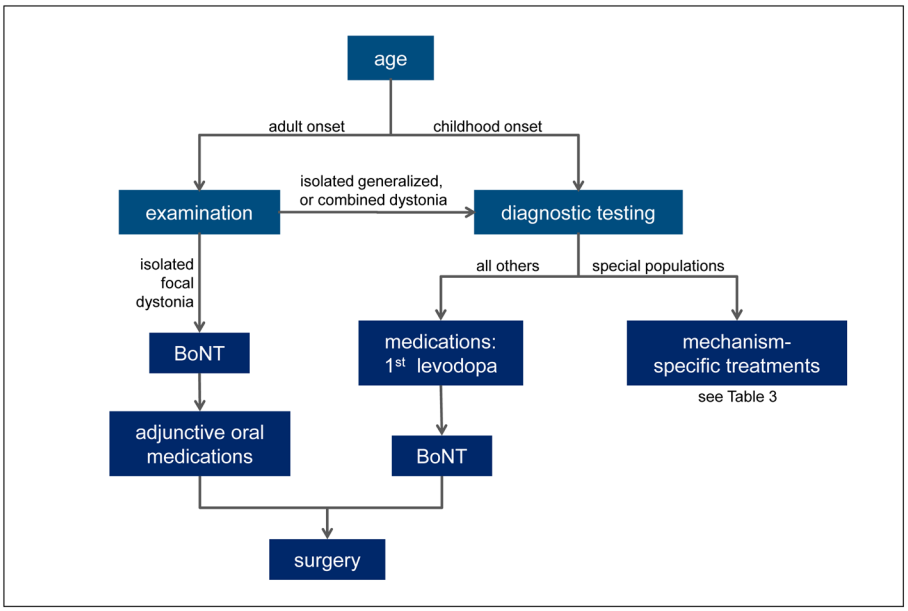

Figure 1.
Methodical strategy for diagnosis of dystonia.

Table 1

Classification of the dystonias according to clinical features

Dimension for classification	Subgroups
Age at onset	Infancy (birth to 2 years)
	Childhood (3–12 years)
	Adolescence (13–20 years)
	Early adulthood (21–40 years)
	Late adulthood (40 years and older)
Body distribution	Focal (one isolated region)
	Segmental (2 or more contiguous regions)
	Multifocal (2 or more non-contiguous regions)
	Hemidystonia (half the body)
	Generalized (trunk plus 3 other sites)
Temporal pattern	Disease course (static vs progressive)
	Short-term variation (persistent, action-specific, diurnal, paroxysmal)
Associated features	Isolated (with or without tremor)
	Combined (with other neurological or systemic features)

Table 2

Classification of the dystonias according to etiology

Dimension for classification	Subgroups
Nervous system pathology	Degenerative
	Structural (typically static)
	No evidence for degenerative or structural lesions
Heritability	Inherited (autosomal dominant, autosomal recessive, mitochondrial, etc…)
	Acquired (brain injury, drugs/toxins, vascular, neoplastic, etc…)
Idiopathic	Sporadic
	Familial

Table 3

Disorders with dystonia that have specific disease-modifying therapies

Disorder	Typical age at onset[1]	Typical characteristics of dystonia	Other typical clinical features[2]	Treatment
Abetalipoproteinemia (Bassen-Kornzweig)	childhood to early adulthood	progressive oromandibular or generalized dystonia	ataxia, chorea, retinitis pigmentosa, fat malabsorption	vitamin E, reduced fat diet
Aromatic amino acid decarboxylase deficiency	infancy	generalized dystonia	developmental delay, hypotonia, oculogyric crises, autnomic dysfunction	dopamine agonists, monoamine oxidase inhibitors
Ataxia with vitamin E deficiency	childhood to early adulthood	rare patients present with dystonia instead of ataxia	ataxia, neuropathy	vitamin E
Autoimmune movement disorders	any age	focal or generalized dystonia	systemic signs of autoimmune disease	address autoimmune process
Biotinidase deficiency	infancy	generalized dystonia	developmental delay, encephalopathy, seizures, sensory defects, skin rash	biotin
Cerebral folate deficiency	early childhood to adolescence	progressive dystonia	developmental delay, neuropsychiatric syndromes, seizures	folinic acid
Cerebrotendious xanthomatosis	late childhood to adulthood	oromandibular or limb dystonia	neurocognitive defects, spasticity, myoclonus, tendon xanthomas	chenodeoxycholic acid
Cobalamin deficiencies (inherited subtypes A-G)	infancy	generalized dystonia	developmental delay, ataxia, spasticity, seizures, bone marrow defects	cobalamin derivatives and/or protein restriction
CoEnzyme Q10 deficiency	any age	some cases present with dystonia and ataxia	varied phenotypes, most often progressive ataxia or encephalopathy	coenzyme Q10
Cerebral creatine deficiency type 3	infancy	generalized dystonia	developmental delay, myopathy	creatine
Dopa-responsive dystonia, classic	early childhood to late adulthood	generalized dystonia	Parkinsonism	levodopa
Dopa-responsive dystonia, complicated	infancy to adolescence	generalized dystonia	hypokinetic-rigid syndrome, oculogyric crises, autonomic dysfunction	levodopa, 5-hydroxytryptophan, and/or tetrahydrobiopterin
Dystonia with brain manganese accumulation	childhood	progressive generalized dystonia	Parkinsonism, liver disease, polycythemia	chelation therapy
Galactosemia	childhood to early adulthood	mild focal or generalized dystonia	ataxia, tremor, food intolerance	lactose restriction
GLUT1 deficiency	childhood to adolescence	paroxysmal exertional dystonia	developmental delay, seizures	ketogenic diet

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Disorder	Typical age at onset[1]	Typical characteristics of dystonia	Other typical clinical features[2]	Treatment
Glutaric aciduria type 1	early childhood to early adulthood	static generalized dystonia following encephalopathic crisis	developmental delay, encephalopathic crisis	avoid or treat aggressively any intercurrent illness, lysine restriction
Homocystinuria	childhood	generalized or paroxysmal dystonia	neurocognitive dysfunction, myopia, ectopic lens	methionine restriction
Guanidinoacetate methyltransferase deficiency	infancy	progressive generalized dystonia	developmental delay, seizures	arginine restriction, creatine and ornithine
Maple syrup urine disease	childhood	focal or paroxysmal dystonia	neonatal encephalopathy, ataxia	leucine restriction ±thiamine
Methylmalonic aciduria	childhood	static generalized dystonia following encephalopathic crisis	developmental delay, encephalopathic crisis, renal insufficiency, pancytopenia	avoid or treat aggressively any intercurrent illness, protein restriction
Molybdenum cofactor deficiency (sulfite oxidase)	adolescence	rare patients present with dystonia and parkinsonism	developmental delay, encephalopathy, seizures	cyclic pyranopterin monophosphate
Niemann Pick type C	early childhood to early adulthood	progressive generalized dystonia	dementia, ataxia, spasticity, seizures, supranuclear gaze palsy	N-butyl-deoxynojirimycin (Miglustat™)
Paraneoplastic movement disorders	any age	rapidly progressive focal or generalized dystonia	malignancy, often occult	address underlying malignancy
Propionic aciduria	early childhood to adolescence	static generalized dystonia following encephalopathic crisis	developmental delay, encephalopathic crisis, optic atrophy, pancytopenia	avoid or treat aggressively any intercurrent illness, protein restriction
Pyruvate dehydrogenase deficiency	infancy	progressive generalized or paroxysmal dystonia	developmental delay, seizures	thiamine, ketogenic diet, dichloroacetate
Rapid onset dystonia-Parkinsonism	early childhood to late adulthood	bulbar or generalized dystonia following encephalopathic crisis	psychomotor disability	avoid or treat aggressively any intercurrent illness, protein restriction
Wilson's disease	early childhood to late adulthood	progressive generalized dystonia	neurocognitive dysfunction, liver disease, Kayser-Fleischer rings	zinc, tetrathiomolybdenate

[1] For most childhood-onset disorders, rare patients may present instead in adulthood.

[2] Some associated clinical features may be attenuated or absent in atypical cases.

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Table 4

Online educational resources for patients

Organization	Internet address
American Dystonia Society	dystoniasociety.org
Bachmann-Strauss Dystonia & Parkinson Foundation	dystonia-parkinsons.org
Benign Essential Blepharospasm Research Foundation	blepharospasm.org
Dystonia Coalition	dystoniacoalition.org
Dystonia Ireland	dystonia.ie
Dystonia Medical Research Foundation	dystonia-foundation.org
Dystonia Medical Research Foundation, Canada	dystoniacanada.org
Global Dystonia Registry	Globaldystoniaregistry.org
National Institute of Neurological Disorders and Stroke	ninds.nih.gov/disorders/dystonias
National Spasmodic Dysphonia Association	dysphonia.org
National Spasmodic Torticollis Association	torticollis.org
ST/Dystonia	spasmodictorticollis.org
The Dystonia Society (UK)	dystonia.org.uk

Table 5

Commonly used oral medications for dystonia

Class of medication	Examples
Anticholinergics	benztropine, biperidin, ethopropazine, ophenadrine, procyclidine, trihexyphenidyl
Dopaminergics	levodopa, pramipexole, ropinirole, tetrabenazine
GABAergics	alprazolam, baclofen, chlordiazepoxide, clonazepam, diazepam
Muscle “relaxants”	baclofen, benzodiazepines, carisoprodol, chlorzoxazone, cyclobenzeprine, metaxolone, methocarbamol, orphenadrine
Others	carbamazepine, cannabidiol, cyproheptidine, gabapentin, lithium, mexilitine, nabilone, riluzole, tizanidine, zolpidem

Table 6

Comparison of the most common botulinum toxin formulations

	OnabotulinumtoxinA (Botox™)	**AbobotulinumtoxinA (Dysport™)**	**IncobotulinumtoxinA (Xeomin™)**	**RimabotulinumtoxinB (Myobloc™)**
FDA-approved indications for dystonia	blepharospasm, cervical dystonia	cervical dystonia	blepharospasm, cervical dystonia	cervical dystonia
Preparation	vacuum dried	freeze dried	powder	liquid
Available dose sizes (units)	100, 200	300, 500	50, 100	1000, 2500, 5000
Storage	refrigerate	refrigerate	room temperature	refrigerate
Approximate dose equivalency*	1	2.5 – 3	1	40

*As the first FDA-approved BoNT, onabotulinumtoxinA was arbitrarily defined as having a strength of 1. The relative strengths of the others are compared against this value.