

# THE MEDICAL AND SURGICAL TREATMENT OF DYSTONIA

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Dystonia may present as an isolated disorder or as part of another disease process. The clinical manifestations of dystonia vary and may involve one body region or many, may start in childhood or adulthood, may be progressive, static, task-specific, paroxysmal or dynamic. Primary dystonic disorders may be inherited or acquired. Often there is no anatomical abnormality, despite the presence of abnormal function.

With the varying etiology and involvement, treatment follows and the treatment plan for each patient should be tailored. The treatments for dystonia change over time and as the dystonia changes in each patient, the treatment plan should also be altered.

There are multiple lengthy reviews describing treatment recommendations. This syllabus was developed as a practical synopsis to complement the slides and videos presented. General diagnostic and treatment strategies are discussed. Then available oral, injectable and surgical options are reviewed.

## **Before Starting Treatment**

The dystonias may be categorized clinically by body region affected, age at onset, temporal aspects and associated features. Each of these categories has important implications for treatment and accurate diagnosis is important because different forms of dystonia may respond best to different treatments. There are also specific treatment options that address underlying mechanisms rather than symptomatic treatment for some patients.

Age at onset is important because childhood onset isolated dystonias are more likely to begin in a limb and progress to generalized involvement or become clearly secondary to a specific etiology. For children and young adults where dystonia seems to be an isolated problem, genetic testing for DYT1 or DYT6 or for Wilson's disease should be considered, particularly if there is a family history. In contrast, adult onset isolated dystonias are more likely to begin in the craniofacial region or neck with limited spread.

For dystonias associated with another neurological or medical condition, there are many potential disorders that may lead to testing. It is not feasible to test for all potential disorders where dystonia may occur and complete or even partial testing is often cost prohibitive. In this case, consultation with a specialist in genetics may be helpful.

The evaluation for most patients with dystonia should include specific and appropriate laboratory testing and a brain MRI. If patients also have signs of parkinsonism, dopamine transporter imaging may be considered. Once the diagnosis of dystonia is made, education about the process is important. Although about 20% of patients with isolated dystonia may go into remission, the vast majority of patients require ongoing management of their condition. Expectations of treatment and determining goals of therapy are areas of discussion in setting up the long term management plans.

## **General Treatment Strategies**

*Focal and segmental dystonias.* For most patients with focal and segmental dystonia, the treatment of choice is botulinum neurotoxin therapy (BTX). Often due to logistical reasons, but also if further work-up is required, BTX is often not administered on the first visit. In patients with focal dystonia, environmental changes or potentially oral agents can be considered. For cervical dystonia, oral agents such as trihexyphenidyl or clonazepam can be considered. Muscle relaxants are often tried but are rarely helpful other than facilitating sleep. Since cervical dystonia is one of the few dystonias often associated with pain, this form of dystonia more often requires adjunctive treatment with BTX. Other focal dystonias such as task-specific dystonia or blepharospasm rarely require adjunctive treatments. Because segmental dystonias are more extensive, the oral therapies are more often used.

Limb dystonias can be the most challenging to treat. Often, smaller doses of BTX are useful, but caution must be used to prevent excessive weakness in an otherwise functional limb. Oral medications are rarely helpful, but levodopa therapy, particularly in children may be tried. Trihexyphenidyl is also sometimes used. If there is prominent tremor component, benzodiazepines are an alternative.

*Generalized dystonias.* For patients with generalized dystonia, it is not feasible to use BTX in all involved body regions. Instead, the initial treatment modality relies on oral medications. Generally, anticholinergics (trihexyphenidyl), benzodiazepines (clonazepam), levodopa and sometimes other drugs are used. If the oral treatments are inadequate, particularly for one particular focal region, then BTX can be considered for that area. When medical with adjunctive BTX therapy is inadequate, surgical options are often considered. Selection of patients is critical in determining the outcome. In addition, patients tend to have a better outcome when the functional neurosurgeon and treating neurologist are experienced in managing the devices used.

## **AVAILABLE TREATMENT OPTIONS**

### **Pharmacologic Treatment**

*Dopamine therapy.* Levodopa is the precursor in dopamine synthesis and readily crosses the blood-brain barrier. In dystonia, the mechanism is thought to involve augmentation of dopamine neurotransmission in the basal ganglia. In children with dopamine responsive dystonia, levodopa therapy is remarkably effective with almost complete resolution of symptoms in low doses. In this rare population, the benefits may last for decades with minimal side effects. Levodopa may also be effective in some adults, particularly those with focal dystonias that involve the limbs. Unlike limb dystonias, however, the more common craniofacial and cervical dystonias of adults do not typically respond to levodopa.

Dopamine agonists, monoamine oxidase inhibitors and amantadine are used in Parkinson's Disease as pro-dopaminergic therapy and may also be considered, although there are limited studies to support the use of these medications.

*Anticholinergics* Trihexyphenidyl, benztropine and others block muscarinic acetylcholine receptors and are thought to influence dystonia at the level of the basal ganglia. These medications are among the most prescribed for dystonia. However, efficacy may be limited due to the high dose needed for clear efficacy and the accompanying side effect profile. Anticholinergic medications have the most evidence (although still limited) in childhood-onset dystonias. Effective doses range from 2-120mg daily of trihexyphenidyl in 3-4 divided doses. Common side effects include sedation, cognitive impairment, constipation, urinary retention, blurred vision, dry mouth, insomnia and restlessness.

*VMAT2 inhibitors* Tetrabenazine is the most commonly used and available VMAT2 inhibitor although other medications in this class are under development, such as deutetabenazine and valbenazine. VMAT2 inhibitors deplete monoamines from pre-synaptic vesicles. The primary neurotransmitter involved is dopamine, but others may be impacted as well. There are small studies to support its use and may attenuate the dopaminergic transmission in the basal ganglia. Although patients with idiopathic dystonia may benefit, those with tardive dystonia may benefit most since tetrabenazine is used for chorea associated with Huntington's Disease, tardive dyskinesia and tics. The dose of tetrabenazine needs to be titrated slowly up to 12.5-200mg daily in 3-4 divided doses. Common side effects include sedation, depressed mood, akathisia, insomnia, parkinsonism and anxiety.

*Benzodiazepines* Clonazepam is the longest acting, but lorazepam and diazepam are also used. Despite the widespread use, there is limited evidence to guide recommendation for type and dose. They may be best for dystonias with a tremor component or those with co-morbid anxiety disorders. Effective doses of clonazepam include 0.5-3 mg daily divided in 1-2 doses. Common side effects include sedation, impaired cognition, worsening gait or depression. In addition, there is a risk for dependency and tachyphylaxis. Abrupt discontinuation or rapid lowering may lead to significant withdrawal symptoms or seizures and in patients with a chronic condition such as dystonia, awareness is important to consider from the outset of using these medications.

*Baclofen* Baclofen is a GABA receptor agonist that may be taken orally or infused intrathecally. There are no studies of baclofen in dystonia despite its widespread use in spasticity. If there is some benefit with oral treatment, intrathecal baclofen can be considered. Effective doses range from 30-120mg daily divided into 3-4 doses. Common side effects include sedation, nausea, loss of muscle tone, dizziness and cognitive impairment. There is also a risk of seizures with doses that are increased or decreased too quickly.

*Other Medications* Antiseizure medications (carbamazepine, gabapentin, pregabalin, acetazolamide), muscle relaxants (carisoprodol, cyclobenzaprine, methocarbamol, tizanidine, dantrolene), cannabinoids and other classes of medications can also be considered in specific refractory cases. Dopamine receptor antagonists are no longer recommended for use in dystonia.

### **Chemodenervation with Botulinum Toxins (BTX)**

BTX therapy has been the focus of many reviews and other educational programs and workshops at the AAN. This summary addresses only a few key aspects for reference. The bacterium *Clostridium botulinum* produces seven distinct toxins, designated A through G. Ultimately, all the neurotoxins produced block presynaptic release of acetylcholine, regardless if it muscarinic or nicotinic. The mechanism varies between serotypes, but typically docking proteins prevent the exocytosis of acetylcholine. When this process occurs at the neuromuscular junction, weakness at the site of injections results. For human clinical purposes, type A (Botox®, Xeomin®, Dysport®) and type B (Myobloc®/Neurobloc®) are used. There are differences in the use of each of the neurotoxins and they are not interchangeable.

For most focal issues or dystonia, BTX is highly effective and the primary treatment option. Most providers can provide relief of dystonia if the dosing, administration method and muscle choice is appropriate. The use of all the BTX for cervical dystonia are supported with several double blind placebo controlled trials. Many are also studied extensively for craniofacial, limb, oromandibular and other dystonias. Typically, the onset takes 2-10 days after injections and the effect typically peaks at 4-6 weeks post treatment. The range of effect is 10-16 weeks. Most patients return for evaluation and possible re-injection about every 3-4 months with less frequent visit for task-specific dystonias. Intervals of less than 3 months is discouraged due to the potential for increased risk of developing immunological resistance, onset of excessive weakness and the development of systemic effects.

One of the strongest determinants of successful therapy is the proper selection of muscles and dose in the appropriate patients. Goals of therapy should also be discussed with the patient and clear before undertaking BTX therapy. The selection of muscles should be based on clinical exam including limb/neck position, hypertrophy and position with exacerbation based on augmentation maneuvers. Once the set of muscles is selected, EMG guidance may help to determine which muscles are functionally most involved in the dystonia. For patients with altered or unusual anatomy, ultrasound guidance may be useful for the administration of BTX. However, if the dystonia produces clear hypertrophy and there is an established response to therapy, EMG or ultrasound may not be necessary. Injections into the limbs should be completed using EMG or ultrasound guidance.

Doses of BTX vary based on the injection site, BTX used, dilution, depth needed and other factors. Therefore, side effects also vary. When injected into the limbs, excessive weakness may be a concern at the site of injection as well as spread to nearby muscles. In the cervical region, main side effects include head droop, swallowing issues and dry mouth. Peri-ocular injections for cranio-facial dystonia may produce ptosis, dry eye or diplopia. Any site injection has the minimal risk of hematoma or infection.

### **Peripheral and Central Surgical Interventions**

*Deep Brain Stimulation (DBS)* DBS is increasingly used in the treatment of many movement disorders, including medically refractory dystonia. Most patients with dystonia, including primary generalized, focal or segmental that do not respond to less invasive methods can be considered for DBS. The most common target is the internal segment of the globus pallidus. A recent review of 24 studies for isolated dystonia in 523 patients found a 65.2% (95% CI, 59.6-70.7) improvement in the Burke-Fahn-Marsden Dystonia scale. Improvements based on the dystonia targeted, outcome measure and degree of pre-surgical responsiveness vary. In two independent trials, there was a 50% improvement in the Burke-Fahn-Marsden rating scale of approximately 50% at three months. The most significant complications include ~1% stroke, infection (immediately post-op and delayed), cognitive change, weakness and dysphagia.

*Ablative procedures* Pallidotomy and thalamotomy have been used for many decades, again for a variety of movement disorders, including various forms of dystonia. In general, DBS has replaced ablative procedures. However, if DBS is not feasible but the patient may benefit from surgical options, it may be considered. MRI-guided focused ultrasound has recently been FDA-approved for essential tremor and may be an ablative option in the future for dystonia as well.

*Intrathecal baclofen* Although some patients with dystonia may not respond to oral baclofen, the dose of baclofen may be limited to due to side effects. Intrathecal baclofen may be an option, particularly if the dystonia primarily impacts the lower extremities. Baclofen is delivered in small doses through a pump which needs to be refilled every one to three months depending on use. Complications may include infection, equipment malfunction, overdose, seizures, CSF leak or withdrawal reactions.

*Other* Chemical myotomy with phenol, myotomy and myectomy are discouraged in dystonia and not generally used with other therapies available today. Selective denervation is now only rarely used by select center as a treatment modality, but can be considered if performed by an experienced clinician.

### **Physical, Supportive and Ancillary Therapies**

Physical therapy (PT) may augment the effect of oral and injectable treatments for dystonia. Rarely will PT be effective as the sole therapy for dystonia. PT can help with range of motion and overall conditioning. Combined with Occupational Therapy (OT) and specific bracing, limb dystonias may also be better managed with bracing, augmentative devices and adaptive equipment. Working with an experienced PT or OT is critical since therapies for dystonia are different than for other neurological diseases. In addition, caution is advised to prevent pain or fatigue. An experienced practitioner will also be able to develop a program that may incorporate a sensory trick or specific devices to suppress symptoms. Similarly, speech therapy can be used with spasmodic dysphonia and laryngeal dystonias.

When considering the theories behind dystonia, immobilization of a limb can reduce the proprioceptive input and has been tried in small clinical trials with limited success. This technique should be used in combination with other pharmaco- and nonpharmacological therapies

### **Specific Treatments for Individual Disease States**

*Wilson's Disease* Approximately 85% of patients have some degree of dystonia and effective treatments are available. Copper chelation therapy can prevent progression and reverse disability. Because Wilson's disease has a fatal progressive course if not treated, it should be excluded with appropriate testing in all children and young adults who present with a progressive dystonia.

*Dopa-responsive dystonia* This form of dystonia presents in childhood and young adults as an isolated dystonia. It often has a diurnal fluctuation with more symptoms in the latter portion of the day. It may progress to become generalized and appear like other disorders such as cerebral palsy. Due to this mimicry and the exquisitely responsive nature of DRD, it is common to try levodopa therapy for most childhood and many young-adult generalized dystonias. Genetic testing is available for the most common mutation in GCH1.

*Paroxysmal dyskinesias* There are multiple forms of paroxysmal dyskinesias, but most have dystonia associated with the episodes. Non-kinesiogenic paroxysmal dyskinesias often have dystonia present inter-ictally. These dystonias will often respond to anti-seizure medications in addition to many of the other oral medications.

### **Summary and Future Prospects**

The dystonias include a heterogeneous group of symptoms and independent diseases. Due to the variety of subtypes of dystonia, each dystonia and patient responds differently to various treatments. There are some special populations of patients who respond well to specific therapies. Although these patients are rare, they should not be overlooked because treatment can be life-saving. For the more common focal and segmental dystonia's, BTX is the treatment of choice. It can be combined effectively with oral medications. BTX may also be used to address the most troublesome features in patients who have a broader distribution of dystonia, such as in the generalized dystonia. For most generalized dystonias, empirical trials with several oral agents can sometimes provide at least partially relief of symptoms. When medical therapy is inadequate, surgery as an option. The successful experiences with DBS in generalized dystonias have led to their increasing popularity and extension to medically refractory segmental and focal dystonias. Although we do not yet have a definitive cure, careful selection of the right combinations of treatments can result in a substantially improved quality of life for most patients.

While many treatment options exist most, most of them focus on symptom control and are not curative. In order to develop more definitive cures, we must about future efforts toward developing a better understanding of the neural processes underlying dystonia. Recent progress in both basic and clinical research has dramatically increased our understanding of the pathogenesis of dystonia at the genetic, biochemical, anatomical and physiological levels.

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