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Update on Treatments for Dystonia

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Abstract

Oral medication, botulinum toxin injections and deep brain stimulation are the mainstays of treatment for dystonia. In addition, physical and other supportive therapies may help prevent further complications (e.g., contractures) and improve function. This review discusses evidence-based medical treatment of dystonia with an emphasis on recent advances in treatment and how the information can be applied to individuals with dystonia.

Keywords

dystonia; treatment; medication; deep brain stimulation

INTRODUCTION

Dystonia is a movement disorder in which involuntary muscle contractions force certain parts of the body into abnormal movements or postures. Dystonia can affect any part or parts of the body, and may result in sustained, rhythmic or task-specific involuntary muscle contractions. Dystonia is classified according to its clinical characteristics and etiology [1•]. Features such as age of onset, bodily distribution and the presence or absence of associated neurologic symptoms contribute to the classification of dystonia. Broadly speaking, age of onset is divided into early (occurring at less than 28 years of age) and late (occurring at 28 years of age or older). Bodily distribution is sub-divided into focal (1 body part affected), segmental (2 contiguous body parts affected), multifocal (2 non-contiguous body parts affected) and generalized (the trunk and at least 2 other body parts affected). Associated neurologic features may include, but are not limited to, tremor or Parkinsonism. On a parallel axis, dystonia is classified according to its presumed or clearly identified etiology. Dystonia may be inherited, such as DYT1 or DYT6 dystonia, acquired due to perinatal brain injury, drug exposure or CNS infection or sporadic, such as in late onset focal dystonias (e.g., cervical or laryngeal). Taken together, the clinical features and data regarding etiology help to determine an optimal treatment plan for each patient.

Treatment

Current treatment options can be divided into: physical and supportive therapy, oral medication, chemodenervation with botulinum toxin and neurosurgical treatment. Each

treatment option will be discussed separately. Then, the approach to particular patients will be discussed, based on the clinical characteristics of dystonia that are exhibited.

Physical and Supportive therapy

Physical therapy is helpful to maintain a full range of motion in the affected body part(s) and prevent the development of contractures. Orthoses, devices that are used to stabilize a body part and/or assist with function, can be helpful in select subtypes of dystonia. We have found that semi-rigid cervical orthoses, such as an Aspen collar, can help provide and improve head position in those with anterocollis. In those with retrocollis, custom-fitted Minerva braces that provide support to the occiput and are attached via Velcro straps to breast and upper back plates, also improve head position. In those with foot dystonia, we have found that a light weight ankle foot orthotic (AFO) may exacerbate dystonia in some and improve gait in others, by facilitating dorsiflexion during the swing phase. Thus, we recommend a trial with an AFO while being observed by an experienced physical therapist or physician to determine its potential utility.

Oral medications

A variety of oral medications provide some relief to individuals with dystonia (Table 1). In all cases of early onset dystonia a trial of dopaminergic therapy, in the form of carbidopa/levodopa, should be initiated. Children with Segawa's syndrome, also known as DYT5 dystonia, typically develop dystonia in a foot that may spread, over several years, to involve other limbs. Walking becomes difficult and displays a diurnal fluctuation with worsening over the course of the day and a marked, sustained improvement to low therapeutic doses of carbidopa/levodopa [2]. Segawa's syndrome is caused by mutations in the GTP-cyclohydrolase 1 gene that encodes the rate-limiting enzyme in the synthesis of tetrahydrobiopterin, an essential cofactor for the activity of tyrosine hydroxylase (TH). Children with deficiency in the activity of TH itself, the rate-limiting enzyme in dopamine synthesis, display a variable phenotype that responds to levodopa supplementation as well [3]. The phenotypic spectrum associated with TH deficiency ranges from limb dystonia that progresses to involve more body parts with a diurnal fluctuation to limb rigidity with trunk hypotonia, developmental motor delay and cognitive dysfunction. Carbidopa/levodopa supplementation improves motor function in those with TH deficiency. While not all forms of early onset dystonia are responsive to carbidopa/levodopa therapy, the initiation of a course of dopamine supplementation is certainly warranted and of minimal risk. The most common side effect experienced by children taking carbidopa/levodopa is stomach upset, which may be minimized or reduced by increasing the dose of carbidopa given with each dose of levodopa. Dopaminergic therapy does not provide significant improvement in those with late-onset dystonia.

For those with either early or late-onset dystonia, treatment with GABAergic agents provides some relief of symptoms. The benzodiazepines, clonazepam, diazepam and lorazepam, are effective although typically the side effect of sedation limits the dose that can be tolerated [4]. Oral baclofen, which activates the GABA-B receptor, is also sometimes used in the treatment of dystonia. In our experience, it is most effective in reducing craniofacial dystonias. In those with dystonia affecting larger muscle groups, such as the

neck, limbs or trunk, the sedating properties of oral baclofen outweigh the anti-dystonic effects. To our knowledge, while oral baclofen is frequently used to treat dystonia, no randomized prospective trials studying its efficacy in primary dystonia have been conducted. Intrathecal baclofen (ITB) has been shown to be effective in reducing spasticity particularly in the legs [5]. ITB has also been studied for the treatment of secondary generalized dystonia, in a mixed population of children with cerebral palsy, anoxic brain injury or neurodegenerative disease [6]. While there was evidence that ITB improved quality of life, ease of care and reduced dystonia in this population, it has not been studied in subjects with primary dystonia. Another GABA agonist that may provide relief in dystonia is zolpidem. Zolpidem displays higher affinity of binding to the GABA-BZ1 receptor than other GABA-BZ receptors, thus making it a more selective GABA agonist than the benzodiazepines. Recent data, from a case series, indicates that zolpidem may be of benefit in primary generalized dystonia and some forms of focal and segmental dystonia [7•]. However, a randomized placebo-controlled study in a larger subject population, with various forms of dystonia is needed to determine if zolpidem provides a statistically significant reduction in symptoms of dystonia.

Trihexyphenidyl, an anti-cholinergic, has been shown to be effective in reducing the severity of dystonia in a double blind, prospective trial [8]. Typically, the total daily dose is limited due to side effects of blurred vision, constipation, dry mouth and cognitive slowing. Children tolerate higher doses of trihexyphenidyl than adults and all patients tolerate the medication best when started at a relatively low dose, for example 2 mg QD, that is gradually increased by 2 mg every 4 to 7 days.

Tetrabenazine (TBZ) is approved in the United States for the treatment of Huntington's chorea. TBZ inhibits the vesicular monoamine transporter 2 (VMAT2), resulting in the depletion of pre-synaptic stores of catecholamines. Retrospective data indicates that TBZ is safe and efficacious in the treatment of dystonia [9]. We find it most effective for the treatment of tardive dystonia.

Many patients may be managed solely with oral medications (Table 1). For any patient with early onset dystonia, we recommend a trial of levodopa. All of the medications described in Table 1 may cause sedation and cognitive blunting, to a varying degree. Those who do not tolerate a given agent may find relief, with fewer side effects, from another medication.

Future Directions

There is a dearth of potential new medications for dystonia in the development pipeline. A recent pilot study on the efficacy of dronabinol, a cannabinoid agonist that enhances the effects of GABA, revealed no improvement in cervical dystonia subjects [10]. Another class of compounds, the metabotropic glutamate receptor 5 antagonists, is being investigated as potential anti-dystonic agents based on their potential to attenuate levodopa-induced dyskinesias in Parkinson's disease [11]. For cases of generalized dystonia caused by the DYT1 mutation, the safety and tolerability of ampicillin is being evaluated in a placebo-controlled trial. As a secondary measure, the investigators will determine any changes to the Burke-Fahn Marsden Dystonia Rating Motor Scale over the treatment period as well (www.clinicaltrials.gov).

Chemodenervation

For the treatment of a variety of forms of focal dystonia, intermittent injection with botulinum toxin (BoNT) is safe and effective [4, 12, 13, 14••, 15•]. BoNT exerts its action by inactivating proteins in the SNARE (soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors) complex, which mediate vesicle fusion and thus are critical for the release of acetylcholine at the neuromuscular junction [16].

BoNT is purified from the bacterium *Clostridium botulinum*, which produces seven different serotypes of BoNT. Each serotype of BoNT has been allocated a letter, A-G. Serotypes A and B are available for therapeutic purposes. Serotype A cleaves SNAP-25 and serotype B cleaves VAMP/Synaptobrevin, two proteins that are crucial components of the SNARE complex.

Three different brands of serotype A and one brand of serotype B are commercially available in the United States (Table 2). The various brands of BoNT have different dosing guidelines and storage requirements. Thus, the different brands of BoNT are not interchangeable. The most important factors in determining the success of treatment with BoNT is appropriate selection of muscles and accurate injection of the correct dose. Muscle selection should be based on a determination of the primary abnormal position of the head and neck and knowledge of the insertion sites of the corresponding muscles, that when contracting produce the abnormal position. In cervical dystonia, multiple studies have shown that physical exam alone is not sufficient in accurately detecting the involved muscles and that the use of electromyography (EMG) improves accuracy of muscle selection and targeting [17–20]. However, the sample size in each study was small. Thus, a larger multi-center trial, with a larger subject population, would be helpful to definitively determine the utility of EMG in the treatment of cervical dystonia. For focal dystonias (especially those limited to the head and neck) and limited segmental dystonias, intermittent BoNT injection alone is often sufficient therapy with minimal, if any, side effects. The American Academy of Neurology has made evidence-based recommendations regarding the use of BoNT for the treatment of dystonia [12]. Specifically, BoNT should be offered as treatment of cervical dystonia or blepharospasm and may be offered for focal upper extremity dystonia and adductor laryngeal dystonia. Treatment with BoNT may also be considered for treatment of focal lower extremity dystonia.

Surgical treatment

The rationale for creating a lesion in the globus pallidus internus (GPi) for the treatment of dystonia arose from the finding that L-dopa induced dystonia in Parkinson's patients improved after pallidotomy [21]. As it became clear that creation of fixed, bilateral lesions in the GPi could result in speech and cognitive dysfunction, attention turned to the use of deep brain stimulation (DBS) to create modifiable electrical lesions to minimize adverse effects while maximizing therapeutic benefit. A caveat to the use of DBS in dystonia is the length of time required to see benefit, which typically occurs over months after the initial surgery.

DBS of the internal segment of the globus pallidus (GPi) has been shown to be efficacious in the treatment of primary generalized and segmental dystonia, in both adults and children, as well as in cervical dystonia and craniofacial dystonia that does not respond to conservative treatment with medication and botulinum toxin injections [22–25]. In children with primary generalized dystonia, DBS of the GPi is now considered a first-line treatment with the goal of reducing loss of mobility and joint deformity. There is limited evidence to suggest that in DYT1 dystonia, implanting DBS earlier in the disease course leads to greater recovery of function [26, 27]. A realistic assessment of DBS efficacy in primary dystonias suggests an efficacy rate of approximately 50% [28]. Recent reports also suggest that with careful selection of subject and type of dystonia, DBS may be effective for secondary dystonias, especially tardive dystonia [29–31]. Further research into alternate DBS targets and stimulation parameters may provide further improvements for those with secondary dystonia.

CONCLUSIONS

The mainstays of treatment for dystonia are oral medications and intermittent injections of botulinum toxin. Cases of focal and segmental dystonia are typically managed by a combination of these two therapeutic modalities, with daily oral medication added in those cases where botulinum toxin injections alone do not provide adequate symptom control. In those with primary dystonia and tardive dystonia for whom such conservative therapy is not adequate, surgical treatment with deep brain stimulation can provide a reduction in symptom severity, by about 50 percent.

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Table 1

Oral medications for treatment of dystonia

Agent	Target Population	Titration and Dosing
Carbidopa/levodopa	Early onset dystonia	Begin 1 mg/kg/day div BID to TID. Increase by 1 mg/kg/week, up to 5 mg/kg/d for at least 4 weeks
Benzodiazepines Clonazepam Diazepam Lorazepam	Early onset dystonia Late onset dystonia	Clonazepam 0.5 – 10 mg QD Diazepam 2 – 100 mg QD Lorazepam 0.5 – 8 mg QD
Baclofen	Craniofacial dystonia Early onset dystonia	Begin 2.5 – 5 mg QHS. Increase by 2.5 or 5 mg QD to total daily dose of 80 mg
Zolpidem	Primary generalized dystonia Craniofacial dystonia Hand dystonia	5–20 mg QD
Trihexyphenidyl	Early onset dystonia Late onset dystonia	Children begin 1 mg BID, increase by 1 mg Q3 to 5 days to maximum of 80 to 100 mg TID. Adults typically tolerate 8 – 12 mg QD.
Tetrabenazine	Tardive dystonia	12.5 – 200 mg QD

Table 2

Botulinum Toxins Available in the United States.

Generic Name	Onabotulinum toxin A	Rimabotulinumtoxin B	Abobotulinumtoxin A	Incobotulinumtoxin A
Brand Name	Botox	Myobloc	Dysport	Xeomin
Serotype	Serotype A	Serotype B	Serotype A	Serotype A
Mechanism of Action	Cleaves SNAP 25	Cleaves VAMP	Cleaves SNAP 25	Cleaves SNAP 25
How supplied	Vacuum dried	Liquid	Freeze dried	Powder
Storage Requirements	< 8°C	< 8°C	< 8°C	< 25°C
Reconstitution	Preservative-free saline	Not Applicable	Preservative-free saline	Preservative-free saline
Dose range for Cervical Dystonia	50 to 300 Units	2,500 to 15,000 Units	250 to 1,000 Units	100 to 300 Units