Botulinum Toxin Treatment of Primary Dystonia

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Introduction

Dystonia is a sustained or intermittent muscle contraction that causes abnormal movements and/or postures [1]. Prevalence of dystonia is difficult to accurately ascertain due to misdiagnosis and/or under-diagnosis. Nutt et al. estimated its prevalence to be 3.4–29.5 per 100,000, though it is higher in certain communities [2–4]. For example, it is five times higher in Ashkenazi Jews relative to the general population [5]. The annual prevalence rate for primary dystonia is 152 per million, and focal dystonia has the highest relative rate at 117 per million. Prevalence rates for specific types of dystonia have been estimated at 28–183 per million for cervical dystonia (CD), 36 per million for blepharospasm (BPS), and 14 per million for writer's cramp (WC) [3, 6].

There are multiple treatments for dystonia including oral medications, intrathecal infusions, and deep brain stimulation (DBS). Choice of treatment depends on the etiology of the dystonia and the extent of muscle involvement. Treatment of generalized dystonia often relies on oral medications, intrathecal infusions, and/or DBS surgery. However, focal dystonia is best treated with injection of botulinum toxin (BoNT) [1]. The first double-blind, placebo-controlled trial demonstrating the efficacy of botulinum toxin type A (BoNT-A) in CD was published in 1986, and since then its use has been expanded to hundreds of different neurologic conditions.

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Multiple subsequent studies have demonstrated that it is an effective and safe treatment for multiple forms of dystonia in addition to CD [7].

Classifying Dystonia

The term "primary" dystonia is historically the most consistently used terminology and usually refers to dystonia occurring without other neurological symptoms or pathologic abnormalities [8]. As dystonia is often associated with other neurologic and psychiatric features, this definition was recently refined [9]. The newest classification of dystonia created a category called "isolated" dystonia in which dystonia is the only motor feature seen, with the exception of tremor [1].

Dystonia can also be classified in terms of its age of onset, body region distribution, and temporal evolution. The exact cutoff between early-onset and late-onset dystonia is debated but in general early-onset dystonia is that which occurs before age 20, and late-onset dystonia occurs in patients older than 20 [10]. Early-onset dystonia usually starts in the lower extremity while late-onset dystonia usually starts in the upper body, particularly the muscles of the neck [2]. Classification by age is important in that early-onset dystonia is more likely to have a discoverable cause and is more likely to generalize [1].

Types of Dystonia

Cervical dystonia (CD) is the most common late-onset focal dystonia. It affects the muscles of the neck and shoulders and can take many different forms including horizontal head turning (torticollis), lateral neck tilting (laterocollis), flexion of the head (anterocollis), extension of the head (retrocollis), and shoulder elevation. About two-thirds of patients will have a combination of these movements. Overlying spasms may cause the head tremor seen in about 14% of CD patients [11]. The average age of onset is in the early 40s and the estimated incidence is 0.8 per 100,000 person-years [12]. Many of these patients also develop focal dystonia elsewhere—16% can have oral dystonia, 12% mandibular dystonia, 10% hand or arm dystonia, and 10% have BPS [11]. Overall, about 23% of patients with CD experience spread of their symptoms to contiguous body regions [13].

BPS is characterized by stereotyped, bilateral, synchronous spasms of the orbicularis oculi muscles. These can be clonic with increased blinking, or tonic with sustained eye closures. The spasms vary in duration, and may include eyelid narrowing or closure [14]. BPS affects approximately 16–133 cases per million [10]. It is more common in women, and has a typical age of onset between the fifth and seventh decades. In almost half (47%) of patients, it spreads to adjacent body areas, often within the first 5 years [13]. It may also be associated with a tremor of the head or upper limbs [14].

Focal limb dystonia starts more commonly in the upper rather than lower extremity in adults. In the sub-category of focal hand dystonia (FHD), writer's cramp (WC) and musician's dystonia are the most common. They are considered task-specific in that the patient experiences the dystonia when performing a specific task, but otherwise has normal use of the involved muscles [15]. It usually appears between age 20 and 50, and affects men and women equally [16]. In WC a pen is often held abnormally and there are multiple abnormal postures of the fingers and wrist that can be seen. One study estimated the rate of spread of FHD into another body site to be 38% [13].

Pathophysiology

There is no neuro-anatomical model described that adequately explains the pathophysiology of dystonia. Secondary dystonia has been seen in tumors, infarcts, hemorrhages, arachnoid cysts, demyelinating lesions, and other lesions in the cerebellum and its associated brainstem outputs as well as in the basal ganglia [17, 18]. Functional MRI studies have noted increased activation in the basal ganglia and cerebellum in dystonia [19]. Within the basal ganglia, putaminal lesions in particular are known to cause dystonia [20]. In one study, the putamen was reported to be about 10% larger in patients with primary dystonia [21].

Argyelan et al. suggested that abnormal connections between the cerebellum and thalamus may predict the penetrance of DYT-1 dystonia [22]. Some studies in genetically dystonic rats have shown higher levels of glutamate decarboxylase messenger RNA in Purkinje cells and decreased levels of the same in the deep cerebellar nuclei [23]. Other animal models have shown that dystonia can be induced with pharmacologic manipulation of the cerebellum [24].

Though its involvement is clear, the precise mechanism by which the basal ganglia is involved in producing dystonia is not known. Given that the most effective pharmacologic therapies for dystonia are anticholinergic and dopaminergic medications, dopamine and acetylcholine systems likely play a role in this disorder [17]. Many patients with Parkinson's disease develop dystonia, further implicating the dopaminergic system. Some recent evidence has shown that impaired reciprocal modulation between striatal dopamine and acetylcholine is an important pathophysiological event in DYT-1 dystonia [25–27].

Hallett et al. proposed a loss of inhibition of motor control, leading to a loss in selectivity and a resultant motor overflow as causing symptoms of dystonia. The clinical features of dystonia are thus related to a failure of surround inhibition, and multiple studies using transcranial magnetic stimulation have demonstrated reduced inhibition and abnormal spread of facilitation at the cortical level [28, 29]. Additionally, abnormal plasticity in sensorimotor circuits has been proposed as causing focal dystonia. The core feature of abnormal plasticity in dystonia is a lack of spatial specificity [29]. This could be secondary to lack of inhibition, but there is also spread of maladaptive plasticity into nearby muscle groups [30, 31].

Treatment

For many years, the treatment of dystonia relied on oral medications that had only modest effect on symptoms. High-dose trihexyphenidyl was found to be effective in the treatment of primary dystonia in the mid-1980s [32]. Other medications are frequently used with modest effect—including baclofen and benzodiazepines [33, 34]. In cases of generalized dystonia which is refractory to oral pharmacologic treatment, intrathecal baclofen has been used, though this seems to be effective primarily in secondary dystonia with associated spasticity or pain [25]. Deep brain stimulation (DBS) is also known to be effective in the treatment of dystonia. Several new mediations, including ampicillin for DYT-1, levetiracetam for myoclonus-dystonia, and perampanel for dystonia are currently being investigated [35, 36].

Botulinum toxin has transformed the landscape of the treatment of dystonia in the past 30 years. It is produced by the bacterium *Clostridium botulinum* and it exerts its effect by inhibiting release of acetylcholine (ACh) from nerve terminals into the neuromuscular junction. It thus prevents neuromuscular transmission, resulting in weakness of the targeted muscles. Under normal circumstances, ACh release into the neuromuscular junction occurs via fusion of vesicles that contain ACh within the pre-synaptic membrane. There is a synaptic fusion complex made of soluble *N*-ethylmaleimide-sensitive factor enhancement protein receptor (SNARE) proteins which facilitates ACh release. SNARE proteins form a complex of three proteins, two of which are specific targets for different serotypes of BoNT. These proteins are syntaxin 1, synaptosomal-associated protein 25 (SNAP-25), and synaptobrevin. These proteins are involved in docking and exocytosis of the ACh-containing vesicles at the presynaptic nerve terminal [37, 38].

There are seven serotypes of BoNT, but only types A and B are commercially available and FDA approved for clinical use [39]. Each serotype has a different complex protein structure and each cleaves specific proteins at specific locations on the SNARE complex. In the US, there are currently three commercially available types of BoNT-A, which targets SNAP-25. These include OnabotulinumtoxinA (Onabot), AbobotulinumtoxinA (Abobot), and IncobotulinumtoxinA (Incobot). The fourth type of BoNT-A, similar to Incobot in that it lacks complexing proteins, has completed phase 3 trials [40]. There is one commercially available type of BoNT-B–RimabotulinumtoxinB (Rimabot)—and it targets Synaptobrevin. Potency varies between serotypes, however, no clear dosing equivalencies between the serotypes have been established [41].

Generalized dystonia requires multiple treatment modalities, and while there is a role for botulinum toxin, it is typically used in addition to oral, intrathecal, or surgical options. In these cases, the most painful or disabling dystonic areas are usually targeted. BoNT is the first-line treatment of BPS, CD, laryngeal dystonia, oromandibular dystonia, and focal limb dystonia [26]. There is level B evidence for use of Onabot and Incobot and level C evidence supporting the use of Abobot in the treatment of BPS. BoNT therapy in BPS produces roughly a 2.5-point improvement on the 4-point Global Clinical Improvement (GCI) scale [42]. The most common side

Table 1 Injection sites and potential side effects of BoNT [38]

Pattern of dystonia	Muscles targeted by injections	Side effects
Blepharospasm	Orbicularis oculi Corrugator supercilii Procerus	Ptosis, dry eye, tearing, diplopia
CD: torticollis	SCM (contralateral) Splenius (ipsilateral) Longissimus (ipsilateral)	Neck weakness, dysphagia
CD: laterocollis	Splenius (ipsilateral) Scalene(ipsilateral) SCM (ipsilateral) Levator Scapulae (ipsilateral) Trapezius (ipsilateral)	Neck weakness, dysphagia
CD: retrocollis	Splenius ± semispinalis (bilateral) Upper trapezius (bilateral)	Neck weakness, dysphagia
CD: Anterocollis	SCM (bilateral) Scalene complex (bilateral)	Neck weakness, dysphagia
CD: shoulder elevation	Trapezius (ipsilateral) Levator scapulae (ipsilateral)	Neck weakness, dysphagia

CD (cervical dystonia)

effects observed are periorbital hematoma in 25%, ptosis in 13–54%, dry eyes in 7.1–13%, and blurry vision in 42% [27] (see Table 1). Recommendations for use of BoNT in BPS are based on two Class II studies supporting use of Onabot and one class I study supporting use of Incobot as "probably safe and effective." Abobot received the designation of "possibly effective" in BPS based on one class II study, and there is insufficient evidence to support the use of Rimabot in this disorder. Incobot and Onabot are considered equally effective in treating BPS based on a class I comparative effectiveness study performed in 2011, and two more recent comparative effectiveness studies (Class I and Class III). Abobot and Onabot are considered "possibly equivalent" in the treatment of BPS [27].

For the treatment of CD, Abobot and Rimabot are supported by Level A evidence and evidence for use of Onabot and Incobot is level B [27]. Incobot improved the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score by almost ten points 4 weeks following injection in one study, and improved severity, disability and pain scores in a second study [43, 44]. Onabot was found to improve CD severity, associated disability, pain, and degree of head turning at rest compared to placebo, but was more likely to produce dysphagia and rhinitis [45, 46]. Commonly involved muscles and BoNT starting doses are outlined in Table 2.

Multiple randomized, double-blind, placebo-controlled trials have proven the efficacy of BoNT in WC. There is level B evidence for use of Abobot and Onabot in the treatment of focal limb dystonia [47]. A study of Abobot in WC reported significant improvements in handwriting scales, writing speed, and symptom severity. All but one of the patients who received Abobot in this study reported weakness of the injected muscles, but most reported persistent benefit and continued treatment 1 year after the initial injection [48]. Although BoNT injections are regarded as the

Table 2 Recommended botulinum toxin doses in CD [29]

Muscle	Onabot (units)	Incobot (units)	Abobot (units)	Rimabot (units)
Sternocleidomastoid	30–50	30–50	100–200	1000–2500
Splenius	50–60	50–60	200–300	2500–5000
Semispinalis	30–40	30–40	60–150	750–1500
Upper trapezius	40–60	40–60	150–200	1000–2500
Levator scapulae	40–60	40–60	150–200	500–1000
Scalene	30–50	30–50	100–200	500–1000

Onabot: onabotulinumtoxinA, *Incobot:* incobotulinumtoxinA, *Abobot:* abobotulinimtoxA, *Rimabot:* rimabotulinumtoxinB

Table 3 Evidence-based recommendations for efficacy of different botulinum toxin formulations [27]

Indication	Level A	Level B	Level C	Level D
Blepharospasm		Onabot Incobot	Abobot	Rimabot
Cervical dystonia	Abobot Rimabot	Onabot Incobot		
Focal hand dystonia		Abobot Onabot		

Onabot: onabotulinumtoxinA, *Incobot:* incobotulinumtoxinA, *Abobot:* abobotulinimtoxA, *Rimabot:* rimabotulinumtoxinB

treatment of choice for spasmodic dysphonia, there have been no randomized clinical trials to establish a recommendation for its use (Table 3).

Some patients may experience clinical benefit as soon as 2 days after injection with BoNT, but the maximal benefit typically occurs 2–6 weeks after injection. After 6 weeks the benefit begins to wane. The usual duration of benefit is between 10 and 16 weeks, and many patients undergo repeat injections every 3 months [39]. Injections are typically started at the lowest possible dose to avoid unwanted side effects, such as those caused by diffusion of the toxin into adjacent muscle groups. In BPS, many patients report dry eyes, bleeding at the injection site, ptosis, and rarely diplopia from weakness of the extra-ocular muscles [39]. In CD, chemodenervation may cause dry mouth, neck weakness, and most commonly dysphagia [27]. The overall rate of dysphagia is 3.4–19.4%, but is dependent upon the brand of BoNT used. Onabot is associated with dysphagia rates between 8.9% and 10.5%, whereas dysphagia can occur in 26.8% of patients receiving Abobot [49]. When using Incobot, dysphagia occurred in 23.4% of patients who received 240 units of toxin and 10.7% of patients who received a smaller dose of 120 units [27]. Regardless of brand, the dysphagia is usually mild and resolves in 2–4 weeks. Patients with anterocollis are particularly susceptible to post-injection dysphagia given the location of the required injections. Injections for focal limb dystonia can result in weakness of the treated limb [39].

Typically BoNT-A is used first in the treatment of dystonia. The specific formulations of the toxin chosen often have to do with factors such as cost, availability to the physician, and physician experience. Electromyography (EMG) or ultrasound (US) can be used, especially in the limbs and neck, to guide the physician into the involved muscles. There is Level I evidence that EMG and US guidance significantly improves injection outcomes [50]. In addition, there are current studies evaluating whether the mapping of motor endplates, where BoNT enters the neuron, will enhance efficacy and reduce side effects. Using motor endplate injections of BoNT may reduce the dose of BoNT necessary for treatment by 50% in CD [51].

It should be noted that despite significant subjective and objective data from clinical trials indicating that dystonia is successfully treated with BoNT, many patients are lost to follow-up. A recent prospective, observational, multi-center, "real world" registry study investigated the efficacy and safety of Onabot in the treatment of CD. It followed 1046 patients with CD who were treatment-naïve (or had not received injections for at least 16 weeks) over three injection cycles. The mean Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS score) in the 479 subjects who completed the treatment protocol decreased from 39.2 at baseline to 27.1 at the final visit. Furthermore, both physicians and patients reported impressions of improvement were increased by the final treatment visit. Despite these improvements, more than half of the patients initially included in the study were lost to follow-up and did not continue treatment with the injecting physician. This may be in part due to the nature of registry studies which have broader subject populations, are longer in duration, and require patients to pay for the medication received. Most of the subjects who withdrew late in the course of the study did receive the full treatment dose but were lost to follow-up—possibly because they did not have the time nor desire to partake in a non-treatment visit. It may also have been that patients who completed the entire study protocol had the more severe disease [52]. Despite these factors, however, it remains unclear why so many patients discontinue what has proven to be a beneficial and safe treatment.

Non-injected formulations of the toxin are also being investigated. In 2013, Lungu et al. studied 24 patients with BPS, adding topical competitive SNAP-25 inhibitor Acetyl-Hexapeptide (AH8) to their BoNT injections. This was a double-blind, placebo-controlled trial in which the primary outcome was time to return to baseline Jankovic Blepharospasm Rating Scale (JBRS) score after BoNT injection and simultaneous initiation of AH8. The study found the medication to be safe and also that the treatment group had a trend toward a longer time until they returned to their baseline JBRS score compared to the placebo group indicating that addition of this medication to the injection could prolong treatment benefit [7, 53].

Conclusion

BoNT is the current treatment of choice for focal dystonia and may be useful for selected areas in generalized dystonia as well. Use of BoNT is supported by multiple studies and its safety and efficacy have been demonstrated multiple times. The major

limitation of BoNT relates to dosing and the occurrence of side effects which are mostly due to spread of the toxin into adjacent muscles. Despite its demonstrated efficacy, there are many patients who discontinue therapy for unknown reasons.

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