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Movement Disorders (A Videnovich, Section Editor)

Botulinum Toxin Treatment of Movement Disorders

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Abstract

Botulinum neurotoxins (BoNTs) are now among the most widely used therapeutic agents in clinical medicine with indications applied to the fields of movement disorders, pain disorders, and autonomic dysfunction. In this literature review, the efficacy and utility of BoNTs in the field of movement disorders are assessed using the criteria of the Guideline Development Subcommittee of the American Academy of Neurology. The literature supports a level A efficacy (established) for BoNT therapy in cervical dystonia and a level B efficacy (probably effective) for blepharospasm, hemifacial spasm, laryngeal dystonia (spasmodic dysphonia), task-specific dystonias, essential tremor, and Parkinson rest tremor. It is the view of movement disorder experts, however, that despite the level B efficacy, BoNTs should be considered treatment of first choice for blepharospasm, hemifacial spasm, laryngeal, and task-specific dystonias. The emerging data on motor and vocal tics of Tourette syndrome and oromandibular dystonias are encouraging but the current level of efficacy is U (undetermined) due to lack of published high-quality studies.

Introduction

Botulinum neurotoxins (BoNTs), produced by *Clostridium botulinum*, due to their multiple mechanisms of action are now widely used in different fields of medicine. Among the seven serotypes of the toxin (A to G), types A and B because of their prolonged mode of action are approved by FDA for clinical use in the USA. The three types of A toxins approved in USA, consist of onabotulintoxinA (onaBoNT-A, Botox), incobotulinumtoxina (incoBoNT-A, xeomin), and abobotulinumtoxinA (aboBoNT-A, Dysport). The type B toxin is rimabotulinumtoxinB (rima-BoNT-B, myobloc.neurobloc). Although the toxin units are not truly comparable for comparative studies, these ratios have been used in clinical trials: 1-U Botox = 1-U xeomin = 2.5–3-U Dysport = 40–50-U Myobloc. The

Chinese toxin Proscine (not approved by FDA) may also have a 1/1 ratio with Botox.

Botulinum toxins exert their action by inhibition of synaptic SNARE proteins (soluble *N*-ethylmaleimide-sensitive factor-activating protein receptor). The function of the SNARE proteins is to help the synaptic vesicles fuse to the synaptic membrane and initiate neurotransmitter release [1]. Inhibition of acetylcholine release has made intramuscular injection of BoNTs a useful tool for treatment of a variety of hyperkinetic movement disorders.

The role of botulinum toxins in treatment of movement disorders

For this review, we have focused on those movement disorders for which high-quality studies (class I and class II) are available. We assessed the quality of the reported studies and the level of the efficacy of BoNTs in the movement disorders according to the assertions of the Subcommittee in Development of Guidelines for the American Academy of Neurology [2]. According to these guidelines, level A efficacy (effective) denotes presence of at least two class I studies. Probably effective (level B efficacy) requires one class I or two class II studies, and level C efficacy requires at least one class II study. Class I study is defined as a placebo-controlled, double-blind study that meets additional six requirements: clear description of study population, randomization, blinding and concealment, primary outcome measure, exclusion and inclusion criteria, and explanation of drop outs. Class II is also a blinded, placebo-controlled study but lacks one of the above-mentioned criteria.

We have reviewed the literature on BoNT therapy in movement disorders up to July 1, 2017 via Yale University School of Medicine library's search engine including but not limited to PubMed and Ovid-SP. Our search terms consisted of botulinum toxin, BoNT, movement disorders, blepharospasm, hemifacial spasm, myokymia, orofacial dyskinesia, cervical dystonia, laryngeal dystonia (LD), tremor, tic, Tourette syndrome, and myoclonus. The three-movement disorders of facial myokymia, spinal myoclonus, and painful legs-moving toes are also included in this review despite the lack of high-quality studies because of the significant emotional and physical impact they have on patients. The clinical categories of movement disorders are presented based on their anatomical topography.

Movement disorders involving the facial musculature

This category includes blepharospasm, hemifacial spasm, facial myokymia, and orofacial facial dyskinesias.

Blepharospasm

Blepharospasm is a focal dystonia of orbicularis oculi muscles characterized by involuntary blinking and repetitive eye closure [2]. Typically, both eyes are involved. The mean age of onset is in the fifth and sixth decades, and women are more commonly effected, with a female to male ratio of 2.8/1 [3••, 4]. Blepharospasm is usually an isolated finding (essential blepharospasm). Secondary blepharospasm, related to brain stem pathology, represents less than 10% of the cases. The main differential diagnosis of blepharospasm in elderly is eye lid opening apraxia while in young people tics of Tourette syndrome and psychogenic blinking are major considerations. Anticholinergic drugs can ameliorate blepharospasm but elderly may not tolerate effective doses that can be as high as or exceed 20 mg/day (in case of trihexyphenidyl). Common side effects consist of hallucinations, cognitive decline, blurring of vision, and autonomic dysfunction.

Botulinum toxin treatment of blepharospasm

The randomized, blinded, high-quality (classes I and and II) trials of BoNTs for treatment of blepharospasm are illustrated in Table 1 [5–10]. Based on these studies, the Guideline Development Subcommittee of the American academy of Neurology [11] designated a level B efficacy (probably effective) for onaBoNT-A (two class II studies) and for incoBoNT-A (one class I study) and a level C evidence (possibly effective) for aboBoNT-A(one class II study) in treatment of blepharospasm. Three comparator studies [7, 9, 10], compared the efficacy of onaBoNT-A with inco- and aboBoNTs. No significant difference was found among these neurotoxins in regard to efficacy for treatment of blepharospasm (Table 2). Long-term studies with botulinum toxins (some exceeding 25 years) have shown maintained efficacy with repeated injections and lack of serious side effects [13••, 14]. In some patients, a small increase in dose may be necessary to maintain the same level of efficacy over time probably due to low levels of neutralizing antibodies [8]. Studies have shown that quality of life also improves significantly after botulinum toxin therapy for blepharospasm [15, 16].

Despite the paucity of high-quality randomized clinical trials (class I), since approximately 90% of the

Table 1. Class I and II clinical trials in blepharospasm

Authors	Study design	Class	Number of subjects	Toxin	Dose (units)	Primary outcome	Assessed at	Results
Jankovic & Orman [5]	Placebo-controlled parallel	II	12	OnaBoNT-A	25/eye	Fahn's 0–4 scale	Week 1	Toxin group improved ($p < 0.05$)
Girlanda et al. [6]	Placebo-controlled parallel split-face	II	6	OnaBoNT-A	20/ eye	BSDI & videotapes	Week 1	Toxin group improved ($p < 0.05$)
Nussgens and	Rudekamper [7]			Comparator crossover	II	212	OnaBoNT-A versus	AboBoNTA
1:4	ratio-Botox:45 U Dysport: 182	Not	defined	Week 1 [8]	Comparable efficacy less ptosis in the onaBoNT-A group ($p < 0.01$)			
Troung et al. [8]	Placebo-controlled parallel	II	120	AboBoNT-A versus placebo	40, 80, 120	Percentage of normal activity in BSDI between toxin and placebo	Week 4	Median difference three doses compared to placebo $p < 0.001$ in weeks 4, 8, 12
Jankovic et al. [5]	Placebo-controlled parallel	I	109	IncoBoNT-A versus placebo	Up to 50 units per eye	Improvement in JRS	Week 6	For JRS
$p < 0.001$). For BDS $p < 0.02$)								
Wabbels et al. [9]	Comparator	I	61	OnaBoNT-A versus Inco-BoNT-A	1:1 ratio 20 or more units per eye	Improvement in BDI, JRS, PGIC	Week 4 and 6	Comparable magnitude of response. No difference

Table 1. (Continued)

Authors	Study design	Class	Number of subjects	Toxin	Dose (units)	Primary outcome	Assessed at	Results
								in PGIC* between two toxins
Saad et al. [10]	Comparator split face	II	48	OnaBoNT -A versus Inco-BoNT-A	1:1 ratio; mean dose 19.1 units/ side	BDI, JRS	4 injection cycles	No difference in efficacy between the two toxins
Reider et al. 2007	Comparator	II	26	onaBoNT-A versus Prosgine (Chinese toxin)	1:1 ratio—2.5 to 5 per injection site	0–5 scale	Weeks 4, 12	No difference between two toxins

BSDI: Blepharospasm Disability Index, JRS: Jankovic Rating Scale, PGIC: patient global impression of change. * In the post hoc analysis, significantly more patients in the Botox group reached higher scores in BSDI and JRS, OnaBoNT-A: Botox, IncoBoNT-A: Xeomim, AboBoNT-A: Dysport. Split-face: toxin was injected on one side of the face and saline on the other side

Table 2. Injected muscles and doses of ona-BoNT-A in OMD [12]

Type of OMD	Lateral pterygoid[a]	Medial pterygoid	Masseter	Temporalis	Digastric	Platysma (if needed)
Jaw opening dystonia	7.5 units (2.5–25)				5 units (1.5–5)	
Jaw closure dystonia		20 units	25 units (5–30)	15 units (5–25)		7.5 (5–10)

[a]Injected intraorally: the needle is inserted between the pterygomandibular raphe medially and to the mandibular ramus laterally, posterosuperior to the last maxillary molar tooth

patients with blepharospasm improve substantially after BoNT treatment, BoNT injections are now considered the first line for management of blepharospasm [3••].

Technical points

Due to the fine structure of orbicularis oculi muscles, injections around the eye are performed with a small 30-gauge needle. The sites of injections during the initial treatment and the start dose vary among treating physicians. Figure 1 shows our initial map of injection and starting doses for blepharospasm. The starting doses are 2.5 units per site for ona- and incoBoNTs at all sites. Our superior-midline injection site is slightly above the eyebrow in order to avoid ptosis.

Hemifacial spasm (HFS)

Hemifacial spasm is an intermittent muscle contraction of half of the face that usually starts in the orbicularis oculi muscle and subsequently spreads to other facial muscles including those of mid- or lower face. These movements can cause significant emotional distress and social embarrassment. Hemifacial spasm is more common than blepharospasm with a cited prevalence of 14.7/100,000 among women, twice the prevalence noted in men [17]. Unlike blepharospasm which is a dystonia, hemifacial spasm is more in line with myoclonus since the electromyographic discharges that correlate with facial spasms usually have a duration of less than 100 ms. Facial tics and focal motor seizures of the face are commonly confused with HFS. The cause of hemifacial spasm in a majority of patients is an anomalous vessel (often small) that presses against the facial nerve as it emerges from the brain stem.

Treatment with benzodiazepines, baclofen, and gabapentin provides minimal relief. Decompressive surgical procedures are effective, but recurrence is not uncommon and surgery is associated with uncommon but potentially serious morbidity (hearing loss, ataxia, cerebellar deficit, brain stem damage).

Botulinum toxin treatment of hemifacial spasm

Despite availability of a large number of open-label studies that strongly support the efficacy of BoNT

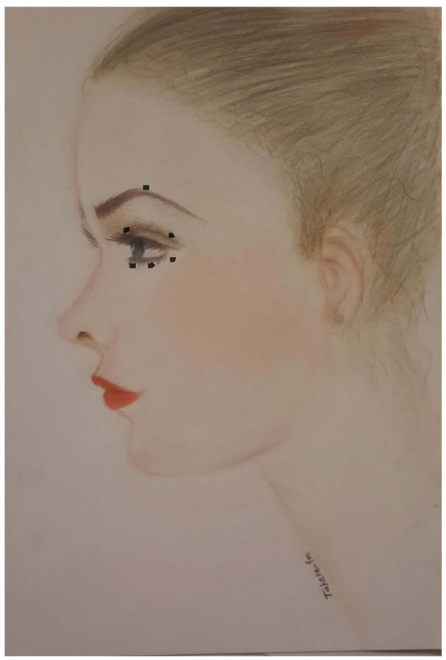

Fig. 1. Authors preferred injection sites for the initial, first-time treatment of Bepharospasm with BoNT. The start dose is 2.5 units in all locations (for Botox and Xeomin). The superior midline injection is given slightly above the eyebrow in order to avoid ptosis. With permission from Springer. From Botulinum toxin treatment in clinical medicine Jabbari B (Editor). Chapter 7: botulinum toxin treatment in multiple sclerosis. Page 116. Drawing from Tahereh Mausavi M.D.

therapy in hemifacial spasm, the number and scope of blinded studies are limited. In 1992, Yoshimura and Aminoff reported the results of the first double-blind, placebo-controlled study of botulinum toxin therapy in hemifacial spasm in 11 subjects [18]. This study showed that 84% of the subjects in the onaBoNT-A group had significant objective improvement of facial movements versus none in the placebo group. Another blinded study, 3 years later, revealed similar results among 42 subjects. Injection of onaBoNT-A into facial muscles resulted in moderate to marked improvement of facial movements in 83% of subjects, but improvement was noted only in 2.5% of subjects in the placebo group [19]. Three additional comparator studies examined the efficacy of two toxins in HFS [20–22]. These studies have shown comparable efficacy between the two toxins (in case of Botox versus Dysport using 1:4, and in case of Botox versus Prosigne using 1:1 ratios). A panel of movement disorder experts, using the AAN criteria [23], concluded that in hemifacial spasm the evidence supports a level B (probably effective) recommendation for onaBoNT-A based on two class II studies and level C (possibly effective) for aboBoNT-A based on one class II study. However, botulinum toxin treatment is now considered the first line of treatment for hemifacial spasm [8]. Studies have shown that 76–94% of patients respond well to BoNT therapy, with satisfactory effects sustained for decades after repeated injections at 3–4-month intervals [24•, 25, 26].

Technical points

Figure 2 shows our starting injection scheme for hemifacial spasm. Injection points around the eye are similar to that of blepharospasm (Fig. 1). We do one 2.5-unit (Botox or Xeomin) injection at mid-face into the zygomaticus muscle. Injections around the corner of the mouth may or may not be needed in the first session, which depends on the presence or absence of significant movements in that area. If needed, we start with 1.25 units for each area around the corner of the mouth (Fig. 2). The dose around the eye and into the zygomaticus muscle may increase to 5 units/site in the subsequent sessions.

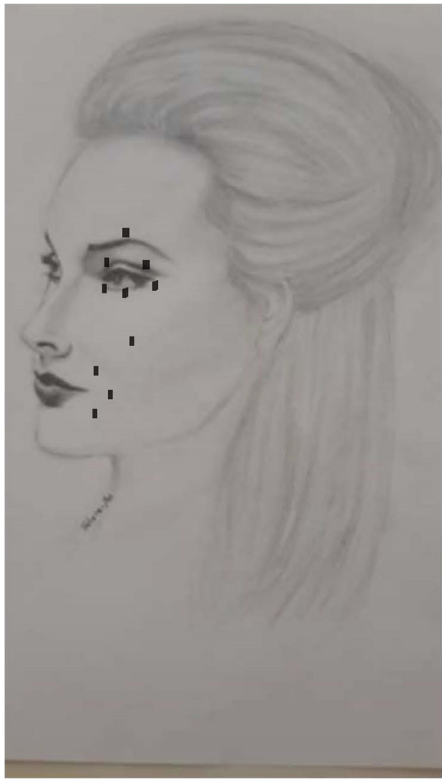

Fig. 2. Authors preferred injection sites for the initial first-time BoNT treatment of hemifacial spasm. The start dose is 2.5 units in all locations (for Botox and Xeomin) except in the lower face which is 1.25 units/site. Lower face injections may be avoided in the first session if movements are not too bothersome.

Facial Myokymia

Facial myokymia is a movement disorder characterized by fine, undulating, rippling movements under the skin [27]. Andermann et al. [28] provided the first detailed description of facial myokymia including the electrophysiology characterized by single motor unit discharges of 50–150 Hz, which often occur in doublets and triplets with a regular frequency of up to several times per second. This differentiates myokymia from fasciculations, facial dyskinesias, and neuromyotonia. Persistent facial myokymia is often caused by multiple sclerosis and pontine glioma, but it also may reflect an inflammatory cranial neuropathy such as seen in Guilain–Barre syndrome. Facial myokymia is painless but can cause significant social embarrassment. Pharmaceutical treatment is not helpful.

Botulinum toxin treatment of facial myokymia

Sedano et al. [29] reported two patients with multiple sclerosis and facial myokymia in whom injection of onaBoNT-A into facial muscles resulted in cessation of movements in 7 days. The first patient, a 26-year-old male, received a total of 10 units of the toxin into the perioral regions (four injections of 2.5 units). The second patient, a 42-year-old male, received five injections,

each 2.5 units, around the left eye. In another communication [30], authors reported a 28 year-old female in whom injection of 2.5 units of onaBoNT-A into each of the following regions, upper lid, lower lid, zygomaticus, and mentalis stopped the myokymic movements in 10 days. In canine post-surgical/post-radiation focal limb myokymia [31], limb myokymia disappeared within 10 days after the injection of ona-BoNT-A into the right biceps femoris and semi-tendinous muscles. The myokymia continued to respond to the toxin therapy, with injections every 3–4 months over a follow-up period of 1 year.

Orolingual, orofacial, and oromandibular dyskinesias

This category includes dystonic or choreo-dystonic movements that can involve the tongue, lips, jaw, and different facial muscles. The dystonic movements of the jaw can present as intermittent jaw opening, jaw closure, or jaw deviation. Lingual movements can take the form of dystonic rolling, tongue retraction, or protrusion. The etiology includes a large number of causative factors, most notable among them being acute drug induced dyskinesias, tardive dyskinesias, and neurodegenerative disorders such neuroacanthocytosis and Wilson's disease. Certain genetically determined dystonias (DyT6 dystonia, Lubag: DyT3 dystonia of the Philippines) also demonstrate mandibular dystonia either as a part of Meige syndrome or without blepharospasm. Pharmacological treatment of orofacial and oromandibular dystonias (OMD) is generally unsuccessful. Administration of anticholinergic agents, anticonvulsants, gabapentin, benzodiazepines, and zolpidem offers partial relief. Deep brain stimulation targeting globus pallidus on both sides has been shown to be effective in some patients with favorable results lasting for years [32].

Botulinum toxin treatment of orolingual, orofacial, and oromandibular dyskinesias

BoNT therapy is now considered the first line of treatment for oromandibular dystonia despite paucity of high-quality clinical trials [8]. Blitzer who reported the first successful treatment of this condition with onaBoNT-A in 1989 has recently published a retrospective review of 59 patients with OMD treated over a period of 16 years [12]. Approximately, 60% of the patients had over 50% functional improvement. Functional improvement was best seen in jaw closure dystonia. The median number of treatments was five, and the average time between treatments was 3.8 months. Repeated treatments of oromandibular dystonia with onaBoNT-A were considered safe and had "minimal morbidity." Rosales et al. [33] have reported the effect of aboBoNT-A (Dysport) injections on OMD of patients with X-linked dystonia parkinsonism of the Philippines (32 jaw opening, 12 jaw closure, 6 jaw deviation). At 4 weeks after injection, the mean dystonia rating scale score was 3 indicating substantial improvement over the baseline.

Technical note

Injections are conducted under electromyographic guidance. Different techniques have been described by different investigators for BoNT injection in OMD. Table 2 shows Blitzer et al.'s advocated technique (intraoral approach for lateral pterygoids) and dose of BoNTs in OMD [12].

At Yale botulinum toxin treatment program, for jaw opening dystonia, we have injected the lateral pterygoid muscles via the external approach in 30 patients. The lateral pterygoid muscle can be located in front of temporomandibular joint, below the zygomatic arch after asking the patient to open the mouth widely. The injected dose varied from 15 to 30 units per side (mean 20 units). In this cohort, 66% of the patients described the treatment very satisfactory in the patient global impression of change (PGIC).

BoNT treatment of lingual dystonia (rolling and retraction) requires caution since overdosing can cause significant swallowing problems. Experienced injectors use usually one of these two techniques: a submental approach or a lateral tongue approach. Nastasi et al. [34], using a submental approach in 30 patients with lingual dystonia, reported significant improvement of dystonia on the OMD "questionnaire – 25" at 4 and 8 weeks following injections (the baseline score of 46 dropped to 38, 4 weeks after injection). Genioglossus muscle was injected submentally with a mean dose of 22 units (onaBoNT-A) divided into four sites. One patient developed moderate dysphagia. At Yale botulinum toxin program, we have treated 12 patients with lingual choreo-dystonic or dystonic movements via a lateral approach. The tongue is held firmly with a gauze close to the tip and pulled out. Injections have been carried out through a 271/2-gauge, three fourth-inch long needle inserted laterally at the mid-point of the tongue. Our starting dose was 5 units (ona-BoNT-A), but in case of a large tongue or severe dystonia, it can be increased to 7.5 units or even 10 units per side. In this cohort, nine patients (76%) have shown 50% or more reduction of

the abnormal tongue movements and expressed high satisfaction with BoNT treatment assessed by PGIC. One patient developed a mild dysphagia which lasted for 4 weeks.

Tongue protrusion dystonia (TPD) is harder to treat. In one report [35], investigators described moderate to excellent response in 55% of 17 patients with TPD after injecting the genioglossus muscle at two finger breadth behind the midline of the body of the mandible and 1–2 cm lateral. The dose of BoNT-A varied from 7.5 to 15 units. One patient who received 15 units suffered from transient severe dysphagia.

Botulinum toxin for treatment for movement disorders of the neck and shoulder region

This category includes a large literature on cervical dystonia and a modest literature on neck and shoulder tics as well as dystonia of the Tourette syndrome and LD.

Cervical dystonia (CD)

Cervical dystonia is the most common form of local dystonia [36], with a prevalence of 5/100,000 [37]. In the CD-PROBE study, a large registry of CD patients, the mean age of onset was 49 years and 74% of the patients were female [38]. Abnormal neck postures in CD takes four major forms: head rotation (torticollis), head tilt (laterocollis), head bent forward (anterocollis), and head bent backward (retrocollis). Torticollis is the most common form of the abnormal head and neck posture in CD followed by laterocollis. Torticollis is sometimes associated with head jerks when the patient attempts to rotate the head opposite to the direction of sustained abnormal rotation. The most common abnormal posture combination in CD is torticollis with laterocollis. Approximately, 70% of the patients with CD have associated neck pain [39]. Anticholinergic medications and baclofen can improve neck posture and pain, whereas clonazepam may alleviate the head jerks. The emerging data regarding efficacy of deep brain stimulation (bilateral GPi) [40••] in CD is encouraging, but the procedure is not devoid of serious complications.

Botulinum toxin treatment of cervical dystonia

Bledsoe and Comella [41] have recently reviewed the literature for high-quality, double-blind, class I studies in cervical dystonia. There were eight studies: three with rimaBoNT-B, three with aboBoNT-A, one with onaBoNT-A, and one with IncoBoNT-A [42•, 43–49]. Additionally, four class I studies [50–53] have compared the efficacy of two toxins (two comparing rimaBoNT-B with onaBoNT-A, one comparing incoBoNT-A with onaBoNT-A and one comparing aboBoNT-A with onaBoNT-A). All placebo-controlled studies have shown efficacy of the studied toxin in improving the posture and related clinical symptoms. Based on existing literature, the Guideline Development Subcommittee of American Academy of Neurology (AAN) in 2016 has given rima- and aboBoNT toxins a level A efficacy (established) and ona- and incoBoNTs a level B efficacy (one class I study each probably effective) [11]. Both ANA guidelines and latest European assessment [11, 36] agree that all four FDA-approved neurotoxins should be considered the first line of treatment for cervical dystonia.

BoNTs also improve the associated neck pain of CD substantially. In the CD-PROBE study that comprised the largest number of studied CD patients to date (1046), 67 and 76% of the patients reported pain relief after treatment with onabotulinum toxin A after the first and third treatment, respectively ($p < 0.002$) [54]. This is consistent with the magnitude of pain relief reported in smaller class I studies of CD using other serotypes of A and B toxins [42•, 43–51]. Whether higher doses of BoNTs are more effective in relieving the CD-associated neck pain or some BoNTs relieve this form of pain better than others is still the subject of investigation. Several authors have noted that in case of rimaBoNT-B, a larger dose (5000 or 10,000 units) was superior to lower doses in relieving the neck pain [47, 48, 55], whereas others did not find a dose specific response with inco- and aboBoNTs pertaining to neck pain relief in CD [43, 56]. All four FDA-approved toxins demonstrated efficacy in relieving the CD-associated neck pain albeit in one study the authors claimed that type B was superior to type A [47], while in another comparator study, AboBoNT-A relieved the neck pain better than OnaBoNT-A [57].

Several open-label studies have indicated improvement of quality of life with BoNT treatment in cervical dystonia. In a randomized, placebo-controlled, blinded study, Mondarin et al. [58] have shown that treatment with 500 units of aboBoNT-A results in improvement of several quality of life subsets of SF-36: physical functioning, pain, general health, and the emotional domain ($p < 0.0.3$).

Neck weakness and dysphagia are the two most concerning side effect after BoNT therapy for patients with cervical dystonia. Dysphagia may be less common in onaBoNT-A therapy (3.4%) compared to the other neurotoxins (12.6, 15.6, and 19.6% with inco-, rima-,

and aboBoNTs, respectively) [36]. Dysphagia is usually mild and disappears after several weeks. Bilateral injections of sternocleidomastoid muscles and injection of higher doses of BoNT into the anterior neck muscles have been associated with higher incidence of dysphagia. The use of EMG and ultrasound is helpful to target the intended neck muscles.

With current formulations of BoNTs, development of non-responsiveness after repeated injections is uncommon. For onaBoNT-A, this low rate (approximately 1%) [59] is due to the reduced albumin content from 25 ng present in the formulations prior to 1997 to only 5 ng in the present formula. Non-responsiveness is rare incoBoNT-A which has a molecule free from antigenic proteins.

Technical note

During the first session, lowest possible dose and fewest number of muscles should be injected. The injector should have a good knowledge of neck's muscle anatomy and the function of each muscle (Table 3). Multiple injections in the neck and shoulder muscles work better than a single injection. Injections should not be placed too low into the sternoceidomastoid muscles (SCM) to avoid injecting the tendon and to diminish the risk of dysphagia. If the injector is used to do injections with patient sitting-up using anatomical landmarks, one should remember that in some subjects, the full silhouette of SCM muscles is hard to see in this position. Lying down with head up, often brings the full muscle into the view.

For isolated and uncomplicated torticollis in a patient with average neck size, we start with 60 units (three sites each 20 units) injected into the SCM and 60 units (divided into three sites) into the splenius capitis muscle (for ona and incoBoNTs). For these toxins, we use a dilution of 10 units/cm^3 []. If head tilt is also a problem additional injections into the ipsilateral scalene (middle), levator scapulae or trapezius may be necessary. EMG and ultrasound are helpful and are definitely required for deeper and more complicated muscles [60, 61].

Table 3. Muscles commonly injected in cervical dystonia

Muscle	Function	Dose range (units)[a]	Suggested starting dose and sites	
Sternocleidomastoid	Contralateral rotator Ipsilateral tilter Anteroflexion	40–100	60	3
Splenius capitis	Ipsilateral rotator Ipsilateral tilter Head extension[b]	40–100	60	3
Splenius cervicis	Ipsilateral rotator Ipsilateral tilter Head extension[b]	20–40	20	1
Semispinalis capitis	Contralateral rotator Ipsilateral tilter Head extension[b]	20–30	20	1
Levator scapulae	Ipsilateral tilter	40–60	40	2
Medial scalene	Ipsilateral tilter Anteflexion	10–20	10	1
Trapezius	Ipsilateral tilter Ipsilateral shoulder elevation Head extension[b]	40–80	40	2
Longus colli [60]	Ipsilateral flexion Anteflexion	10 Injected under ultrasound with EMG guidance	10–25	1

[a]The units depicted in the table are for ona-BoNT-A (Botox) and incoBoNT-A (Xeomin). For AboBoNT-A, the units are approximately 2.5 to 3 times higher and for the rimaBoNT-A 40–50 times higher
[b]Head extensions results from muscle action on both sides

Laryngeal dystonias and voice tremor

LD/spasmodic dysphonia (SD) is a dystonia of laryngeal muscles arising from overactivity of either the thyroarythenoid or posterior cricoarythenoid muscles. The thyroarythenoid muscle hyperactivity leads to over-adduction of vocal cords (adductor dystonia) during speech and presents with strain-strangles, tremulous, harsh, and staccato-like voice with inappropriate pitch and pitch breaks. The less common abductor type that illustrates hyperactivity of posterior cricothyroid muscles manifests with breathy, hypophonic, and whispered speech due to prolonged abduction of vocal cords. Less common mixed types also exist. Other manifestations of LD are stridor (11.9%), dystonic cough (6.2%), dyscoordinate breathing (4.1%), and paroxysmal hiccups (1.6%) [62]. Adductor LD dystonia comprised 82% of the Blitzer's reported cohort of 1300 patients from his 24 years of experience with LD [63]. Among the affected patients with LD, women comprise 63–68% and 12–16% report a family history of dystonia [63, 64]. Pharmacological treatment of LD in general is disappointing. Clonazepam and baclofen may offer modest relief. As for voice tremor, drinking alcohol also improves phonation in LD [65]. In a recently published open-label trial of 23 patients, sodium oxybate, an oral agent with alcohol-like action, has improved the symptoms of LD [66].

Botulinum toxin treatment of laryngeal dystonia

The efficacy of BoNT therapy in improving phonation of the patients with SD has been shown in a single, small double-blind study (one class A) [67] leading to designation of a B efficacy level (probably effective) by the Guideline Development Subcommittee of AAN. BoNT therapy however is currently considered the first line of treatment for LD based on ineffectiveness of other modes of therapy and the high percentage of patients (close to 90%) who have responded in open-label studies with large cohorts.

Technical points

Injections can be done intraorally or intranasally through a laryngoscope or percutaneously. The percutaneous, external approach is preferred by most injectors. It uses a special EMG needle, which both records and allows injection through its hollow core. For the adductor type, the more common form of LD, the needle aims at the thyroarythenoid muscle. The tip of the needle is placed close to the midline at the thyrocricoid membrane (between the thyroid and cricoid cartilage). After gently passing the membrane, the tip is directed 30° superiorly and 30° laterally until it reaches the muscle. Patient may activate the muscle by saying "ii" or "hiss." The toxin is then injected into the muscle after hearing typical sounds in the EMG unit. For the abductor type, the injection is given posterior into the posterior thyroid lamina [68]. Most of the literature on BoNT therapy for LD is with onaBoNT-A (Botox). In adductor LD, starting doses of 0.5 to 1 unit of this toxin are recommended for bilateral injection. The dose can be higher with unilateral injection and can be adjusted with repeated injections. Recent data indicate that other BoNTs are also effective. For aboBoNT-A (Dysport) and rimaBoNT-B (myobloc/neurobloc), ratios of 3/1 and 40–50/1 are recommended (compared with onaBoNT-A units). In a study of 32 patients with SD comparing the effects of type A and type B toxins, the authors found a faster action for type B when used at a 52/1 ratio (effect onset was 2 days for B and 3.2 days for A), but type B demonstrated a shorter duration of action (10.8 versus 17 weeks) [69]. Breathiness of the voice, which may last for couple of weeks, is a common complain after BoNT therapy of LD. Patients usually find it tolerable and not a major issue considering the magnitude and duration (4–6 months) of voice improvement that they experience BoNT injections.

Tics of Tourette syndrome

In 1984, Jankovic first reported that intramuscular injection of BoNT-A (Botox) can markedly improve focal tics and even the urge to move in 10 patients with Tourette syndrome. Half of the patients had neck and shoulder tics in whom injections (75–200 units) were performed into splenius capitis, trapezius, and rhomboid muscles [70]. A randomized, blinded study with a crossover design was conducted in 18 patients with focal tics among whom 14 had Tourette syndrome [71]. Injection of BoNT-A (Botox) into neck and shoulder muscles resulted in significant reduction of focal tics compared to the placebo (39% reduction versus 5.8% increase $p = 0.0007$); BoNT injection also decreased the urge score ($p = 0.02$). In a patient with Tourette, vocal tics, its frequency, intensity, loudness, and urge to make noise were reduced after bilateral injection of BoNT-A (Botox), 1 unit/side, into the thyroarythenoid muscles [65]. Trimble et al. also described a 34-year-old man in whom coprolalia and laryngeal tics improved significantly after injection of 3.75 units of aboBoNT-A (Dysport) into the thyroarythenoid muscles bilaterally [72].

Comment

One randomized blinded study (class II) has shown that injection of BoNT into the neck and shoulder muscles reduces the frequency and intensity of dystonic tics in Tourette syndrome (level C efficacy possibly effective) along with urge to move score. The claim of case reports denoting improvement of vocal tics and copralalia after injection BoNT-A to the thyroarytenoid muscle requires verification by blinded studies.

Botulinum toxin treatment of the upper limb involuntary movements: tremor, task-specific dystonia and focal limb dystonia

Tremor

Essential tremor Essential tremor (ET) is defined as a clinical disorder manifested by bilateral, largely symmetric, postural, or kinetic tremor, involving the hands with variable combination of midline tremors (head, face, and vocal cord) in the absence of abnormal posturing, task specificity, or position dependence [73, 74]. The AAN assigned a level A evidence (effective) to propranolol and primidone and a level B evidence (probably effective) to topiramate, gabapentin, atenolol, and alprazolam in management of ET [75]. Pharmacological treatment of ET however has a high rate of treatment failure, up to 55% [76]. Deep brain stimulation of thalamus is effective in ET but many patients dislike surgery and the procedure can have, albeit uncommonly, serious complications.

The effects of BoNT treatment on ET have been investigated in three randomized, double-blind, placebo-controlled trials, two published as full manuscripts. The first study reported from Baylor College of Medicine [77] assessed the effect of onaBoNT-A (Botox) on ET in 25 patients using unified tremor rating assessment, functional rating scale, sickness impact profile, and accelerometry over a period of 16 weeks. The total injected dose was 50 units with 15 units injected into each wrist flexor and 10 units into each wrist extensor. If there was no response at 4 weeks, the dose was doubled in those muscles (total of 100 units). Significant improvement was noted in the tremor rating scale for the group that received onaBoNT-A treatment. Seventy five percent of the patients in the toxin-treated group and 27% of the patients in the saline-treated group considered their improvement significant. The main side effect was finger weakness which predominantly affected the finger extensors 4 weeks after injection; manifesting with a moderate intensity in 42% of the treated subjects. Five years later (2001) [78], a group from Columbia University in New York published the results of a multicenter study on 133 patients with ET stratified into low and high-dose BoNT treatment groups (50 and 100 units). The same four muscles were injected as those of the Baylor study. Investigators have assessed tremor severity rating, functional disability, quality of life, and grip strength over 16 weeks. Postural tremor improved significantly at 6, 12, and 16 weeks in both low-dose and high-dose groups but several patients in the high-dose group developed pronounced finger weakness. A customized injection approach meeting patient's needs and avoiding injection of finger extensors has been suggested as a reasonable strategy to reduce the incidence of finger and hand weakness noted in these studies [79].

Our group at Yale conducted a double-blind, placebo-controlled study with incoBoNT-A (Xeomin), using a customized injection approach in ET in 30 patients. Eight to 12 muscles selected by careful EMG screening were injected using a total of 80–120 units. Biceps, triceps, pronator teres, finger flexors, and lumbrical muscles that were not included in the previous studies were also injected in this study. The preliminary results of this study showed significant improvement of tremor in the toxin-treated group (12 of 19) compared to the placebo-treated group (2 of 19) ($p = 0.019$). Patients in the toxin-treated group also reported much more satisfaction with treatment than the saline group (10 out of 19 versus 3 out of 19, respectively, $p = 0.031$). Notable hand weakness occurred in 4.8% of the patients [80••].

Tremor of Parkinson's disease (PD)

The published data on the tremor of PD is limited to a few open-label, one single-blind, and one double-blind study [81–83]. These studies collectively indicate that injection of onaBoNT-A into forearm muscle diminishes the amplitude of resting and postural PD tremor although not as robust as seen in the ET. Transient finger and hand weakness in the substantial number of patients was reported in open-label and fixed-dose studies.

We have recently reported the results of a double-blind, crossover study which assessed the efficacy and safety of in 30 patients with tremors (rest and postural) associated with PD. [84] The pattern of injection was customized with injections performed under careful EMG guidance into 8–10 affected muscles. The change in Unified Parkinson Disease Rating Scale (UPDRS) was significant for both rest and action/postural tremors at

both 4 and 8 weeks ($p < 0.01$and < 0.05, respectively). The UPDRS question 16 (activity of daily living) showed significant change in favor of incoBoNT-A compared to the placebo group at 4 and 8 weeks ($p < 0.01$). PGIC also demonstrated significant improvement in favor of incoBoNT-A at 4 and 8 weeks ($p < 0.01$). There was a trend towards improvement in the quality of life (PDQL), in the incoBoNT-A group compared to the placebo group at 8 weeks following injections ($p = 0.06$). A moderate hand and finger weakness was noted in 6.6% of the patients.

Identification of muscles for treatment of ET and PD tremor through incoBoNT-A use kinematic approach has been emphasized in a recent open-label publication which assessed the efficacy of incoBoNT-A in 28 PD and 24 ET subjects [85]. The subjects received six sets of injections over a 96-weeks period. Significant reduction of tremor amplitude was noted in 70 and 76% of PD and ET tremors, respectively. Over the study duration of 96 weeks, 14% of the patients in the PD group and 8% in the ET group withdrew from the study due to development of hand weakness.

Focal hand dystonia and task-specific dystonia (TSD)

TSD is the most common form of focal hand dystonia. Focal hand dystonia can occur during a variety of tasks such as writing, playing music, and sport-related activities. The major clinical types among occupational dystonias are writer's cramp, writer's dystonia, and typists' dystonia. Among musicians, pianists, string and brass/wood wind players, as well as singers are often affected. In the sport category, golfers may develop hand and wrist dystonia (golfer's yip) in the upper limb and runners in the lower limb [86]. Five double-blind, placebo-controlled clinical trials assessed the efficacy of BoNTs in TSDs [18, 87–90]. In three studies, all patients had writer's cramp [87–89]. The fourth cohort consisted of subjects with writer's cramp and musician's dystonia [90] while in the fifth study, subjects had both task-specific and non-TSDs (stroke, PD) [18]. The results of these studies with small cohorts (class II and class III) indicate that writers' cramp and musicians' dystonia improve with BoNT treatment although the magnitude of response is not as robust as observed in other focal dysotnias (cervical dystonia, blepharospasm). While patients experienced improvement of TSD, the initial level of artistic capability does not totally return following BoNT therapy [91].

Surprisingly, very little is published regarding the use of BoNT in non-task-specific focal limb dystonias. In Yakumora and Aminoff's study [18], of task-specific and non-TSDs, two patients with PD and stroke responded well to BoNT therapy, similar to TSDs. A group of movement disorder experts designated a level B evidence (probably effective) for use of ona- and aboBoNT-As in TSDs and recommend this mode of treatment for TSD [23].

Technical note

Injections should be done under careful EMG or ultrasound guidance to locate the specific muscle(s) of interest since the muscles are tightly clustered together in the forearm. The initial dose needs to be small to minimize muscle weakness that can impair fine motor movements needed for delicate tasks. For flexor digitorum communis (FDC), a muscle which is often injected in TSDs, initial doses of 2.5–10, 40–60, and 75–150 units have been recommended for onaBoNT-A, aboBoNT-A, and rimaBoNT-B, repectively [92]. For writer's cramp, the recommended mean total dose for onaBoNT-A is 24.9 units and for aboBoNT-A, 82 units [86, 92].

Botulinum toxin treatment of lower limb involuntary movements

Focal lower limb dystonia

TSD is uncommon in lower limb where most focal dystonias are secondary to stroke or neurodegenerative disorders (PD, Wilson, others). Runners' dystonia can be seen in the lower limbs as a rare example of TSD. Despite lack of clinical trials, in clinical practice, it is recognized that lower limb dystonia, at least partly, responds to BoNT therapy. In case of foot dystonia, treatment success requires EMG or ultrasound screening of the affected muscles (posterior tibialis, gastrocnemius, soleus, flexor digitorum). Larger proximal muscles may not require electrophysiological or ultrasound screening. The dose is variable and depends on the size of the muscle, magnitude of dystonia, and associated spasticity. For instance, for flexor digitorum longus, the following doses have been recommended for ona-, inco-, and aboBoNT-A 10–125, 10–40, and 80–200 units, respectively, and for rimaBoNT-B, 500–3000 units [92]. Higher doses are required for the larger proximal lower limb muscles.

Painful legs, moving toes

The syndrome of painful legs, moving toes (PLMT) is characterized by involuntary toe and foot movements associated with pain in the foot and lower leg [93]. Electromyography often shows a pattern of myokymia in the moving muscles. Movements may start in one leg first and then develop in the other leg supporting participation of a central loop in genesis and maintenance of the movements. Many patients have a history of peripheral trauma to the nerve, plexus, or root [94].

In 2008, we reported two patients with this syndrome in whom injection of onaBoNT-A into the moving muscles (identified by EMG) resulted in marked reduction of movements and improvement of the leg pain [95]. One of the patients received 12.5 units into the flexor digitorum longus bilaterally while the other patient received 50 units into each gastrocnemius and 45 units into each flexor digitorum brevis muscle. Subsequently, two other case reports described similar results with BoNTs in PLMT syndrome. No randomized clinical trials or long-term follow-up reports are available on BoNT treatment of this syndrome.

Spinal myoclonus

Spinal myoclonus consists of a rhythmic and sometimes jerky movements of the lower limbs caused by spinal cord pathology. In less common cases when the lesion is high in the spinal cord, upper limbs may also be involved. Treatment is usually unsuccessful. Clonazepam and diazepam are partially helpful but alleviation of movements may require large doses that cause excessive sedation. Cessation of spinal myoclonus after botulinum toxin treatment was first reported in a 16-year-old girl who developed thoracic cord infarct at age 11 secondary to a cardiopulmonary venous anomaly-Scimitar syndrome [96]. At age 15, she developed rhythmic painful contractions of the left vastus medialis and left rectus femoris with a frequency of 0.5–1 per second. Her examination showed paralysis and atrophy of the right leg with mild weakness of the left leg and bilateral Babinski signs. A total of 280 units of OnaBoNT-A were injected into the left quadriceps muscles (rectus femoris 100 units, vastus medialis 90 units, vastus lateralis 90 units). After this treatment, all movements stopped within 7 days along with marked reduction of her thigh pain. Movements and pain returned after 5 months when a reinjection with the same dose produced the same effect. Lagueny et al. [97] reported similar favorable results with BoNT treatment in a patient with stimulus sensitive spinal myoclonus.

Conclusions

BoNTs have established efficacy at level A in cervical dystonia, blepharospasm, and hemifacial spasm. They are probably effective with level B efficacy in LD, TSDs, ET, and PD-specific rest and postural tremor. The emerging data on a variety of other movement disorders is encouraging, but proof of efficacy of BoNTs in these involuntary movements requires new results from randomized and blinded clinical trials.

Compliance with Ethical Standards

Conflict of Interest

Yasaman Safarpour declares no conflict of interest.
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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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