Botulinum toxin in the management of blepharospasm: current evidence and recent developments

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Abstract: Blepharospasm is a focal (although usually bilateral) dystonia of the orbicularis oculi muscles, producing excessive eye closure. This produces significant disability through functional blindness. Botulinum neurotoxins (BoNT) have become the treatment of choice for blepharospasm; the impressive response rate and the tolerable safety profile have been proven through multiple clinical studies. There are currently four BoNT approved in the United States for different indications - we review the data on blepharospasm for each of these drugs. Currently, incobotulinumtoxinA and onabotulinumtoxinA have the most evidence of benefit for patients with blepharospasm. Current evidence, recent development and future directions are discussed.

Keywords: botulinum toxin, Botox, Xeomin, Dysport, Myobloc, blepharospasm, dystonia, chemodenervation

Generalities

Blepharospasm is a focal dystonia characterized by involuntary closure of the eyelids [Stacy, 2007]. It usually affects both orbicularis oculi, and can progress into causing significant disability. It may occur in isolation, or be associated with other dystonias. Parkinsonism, dystonic cerebral palsy, and tardive phenomena are some of the commonly associated disorders. Adequate treatment of blepharospasm is necessary to allow maintenance of quality of life, avoid functional blindness, and to prevent complications such as corneal abrasions and dermatochalasis. In 1989, blepharospasm (in patients older than 12 years old) was the first indication approved by the United States Food and Drug Administration (FDA) for the use of BoNT-A [Ramirez-Castaneda and Jankovic, 2013]. Before the introduction of chemodenervation through botulinum neurotoxin (BoNT) injections, treatment was challenging, as oral medications had minimal effectiveness and produced limiting side effects. We provide here an up-to-date review of the use of BoNT for blepharospasm.

Epidemiology

Prevalence estimates of blepharospasm range from 16–133 cases per million [Defazio and

Livrea, 2002]. However, most prevalence studies use treatment-based data and therefore likely underestimate the actual prevalence of blepharospasm present in the community. One study reported the incidence of benign essential blepharospasm to be 4.6 cases per 100,000 per year [Bradley *et al.* 2003], while another study reported the incidence of blepharospasm to be 4.6 per 1,000,000 per year [Nutt *et al.* 1988].

Tanner and colleagues reported in 2013 on a large study completed in an integrated health maintenance organization, which included information on 741 patients with incident dystonia. Blepharospasm was found to be the most incident primary dystonia, with an incidence of 1.7 per 10⁵ person-years [Tanner *et al.* 2013]. This study provides a glimpse at the real burden of blepharospasm, underlining the extreme likelihood of prevalence underestimation. Like other dystonias, blepharospasm is more common in women than in men [Tanner *et al.* 2013; Jankovic and Ford, 1983]. Men with primary blepharospasm tend to develop symptoms at an earlier age.

The mean age of onset of blepharospasm is the mid-1950s, and the risk of developing blepharospasm

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increases with age [Defazio and Livrea, 2002]. One age-specific estimate showed a prevalence of 26.6 per 100,000 in people aged 50–69, 31.9 per 100,000 in people aged 60–69, and 74 per 100,000 in people over age 69 [Defazio *et al.* 2001]. Possible risk factors for the development of primary adult-onset dystonia include family history of dystonia and postural tremor and prior significant head or facial trauma, while hypertension and smoking cigarettes appear to be protective [Defazio *et al.* 1998]. For blepharospasm specifically, prior history of eye disease is a possible risk factor, while drinking coffee might be protective [Defazio *et al.* 2011].

Phenomenology

Blepharospasm often begins as excessive blinking, usually accompanied by feelings of dryness or irritation of the eyes. Then it can progress into clonic and finally sustained tonic eyelid closure which can interfere with daily activities [Fahn *et al.* 2011]. Left untreated, blepharospasm can be disabling to the point of rendering a person functionally blind. It may be unilateral at onset, but it almost always affects bilateral orbicularis oculi muscles. Blepharospasms are usually non-task-specific [Torres-Russotto and Perlmutter, 2008]. However, as other dystonias, they can have task-specific improvements and exacerbations. It is often exacerbated by bright lights, reading, and watching television [Grandas *et al.* 1988]. Like other dystonias, blepharospasm may be alleviated by sensory tricks including touching the eyes [Loyola *et al.* 2013], the upper face, speaking, or even singing [Weiner and Nora, 1984].

Phenomenology differential includes non-dystonic excessive eye closure (as that seen in sicca syndrome), tic disorders, hemifacial spasm, apraxia, and psychogenic among others. After the onset of blepharospasm, symptoms generally progress over the first few months to years before stabilizing [Stacy, 2007]. Spontaneous remissions can occur in a minority of patients, but symptoms almost always return.

Blepharospasm pattern of spreading might be different than other dystonia conditions. It may occur in isolation, or affect the lower face [Stacy, 2007]. A segmental dystonia that involves the lower and upper face is usually called Meige syndrome. Symptoms are more likely to spread beyond the orbicularis oculi in patients who are women, have an older age at onset, or have a history of significant head or facial trauma [Defazio

et al. 1998]. In a retrospective series of 602 patients with primary dystonia, blepharospasm was found to spread in 31% of the cases beyond the head area, at a rate more often than other dystonias [Weiss *et al.* 2006]. Therefore, blepharospasm has been commonly associated with dystonia in other parts of the face, neck, trunk, or limbs [Jankovic and Ford, 1983]. There is also a difference on the timing of the risk of spreading of blepharospasm in comparison with other dystonias, as most spread occurs in the first 2 years of blepharospasm, whereas the risk of spread seems constant in cervical dystonia [Weiss *et al.* 2006]. Blepharospasm is often a primary dystonia with no clear underlying cause, but it may also occur secondarily to neurodegenerative diseases, structural brain lesions, or exposure to neuroleptic medications [Grandas *et al.* 1988].

Pathophysiology

Like many disorders, dystonia is likely caused by a combination of genetic susceptibility and environmental exposures. This double-hit theory has been advanced in blepharospasm in an animal model of craniofacial dystonia. In that model, striatal dopamine deficiency caused by a prior injection of 6-OHDA (6-hydroxydopamine) made rodents vulnerable to a simple peripheral injury that leads to the development of facial twitches that mimic cranial dystonia [Schicatanio *et al.* 1997]. Either lesion alone was not enough to produce dystonia.

Classified as a hyperkinetic movement disorder, dystonia is characterized by an excess of movement. This excess is reflected in the cocontraction of agonist and antagonist muscles, overflow of activity into unwanted muscles, and prolonged muscle bursts seen on EMG recordings of dystonia [Cohen and Hallett, 1988]. The pathophysiology of dystonia including, but not limited to, blepharospasm is thought to involve a combination of loss of inhibition, abnormal plasticity, and sensory dysfunction.

Loss of inhibition at many neuroaxis levels allows excessive unwanted movement resulting in the clinical manifestation of dystonia. The unwanted cocontraction of antagonist muscles is a manifestation of the loss of reciprocal inhibition, the process by which the antagonist muscle is inhibited during agonist contraction, which occurs at the spinal level [Stacy, 2007]. Loss of inhibition in the brainstem has been demonstrated by

hyperexcitability of the blink reflex in blepharospasm specifically [Berardeli *et al.* 1985]. Studies using transcranial magnetic stimulation (TMS) show loss of inhibition at the cortical level [Ridding *et al.* 1995]. Surround inhibition is the process by which other possible movements are suppressed in order to allow a more exact voluntary movement, and this has been found to be abnormal in focal hand dystonia [Sohn and Hallett, 2004].

Abnormal or 'excessive' plasticity also contributes to the pathophysiology of dystonia. Task-specific dystonias are associated with repetitive use, and their emergence is often preceded by a period of intense training [Roze *et al.* 2009]. This points to a maladaptive response of the central nervous system as a factor for the development of dystonia [Torres-Russotto and Perlmutter, 2008]. Studies using TMS in dystonia show exaggerated cortical excitability [Quartarone *et al.* 2003], further supporting the role of abnormal plasticity.

Defects in sensorimotor integration are an important component of dystonia's pathophysiology, as could be inferred by the common occurrence of sensory tricks. The role of sensory inputs in dystonia can be demonstrated by the application of vibration which induces hand dystonia in specific settings, while this dystonic response is alleviated with application of lidocaine [Kaji *et al.* 1995]. Focal hand dystonia has been mimicked in monkeys who are overtrained in a specific hand movement [Byl *et al.* 1996]. The brains of these monkeys displayed abnormal reorganization of the sensorimotor cortex compared with healthy controls. Moreover, people with focal dystonia have decreased spatial and temporal discrimination, even in unaffected body parts [Bara-Jimenez *et al.* 2000; Scontrini *et al.* 2009]. In addition, somatotopic representation of the sensory cortex is disrupted in focal hand dystonia [Nelson *et al.* 2009; Bara-Jimenez *et al.* 1998].

Management

Although BoNT has become the most commonly used therapy for blepharospasm, the treatment armamentarium for patients with this condition includes oral medications, physical measures topical treatments, and surgical interventions. Patient education, avoidance of possible causal drugs (such as dopamine blockers), prevention of eye and corneal injury, and supportive care is a fundamental aspect of the management of these focal

dystonias. Some patients find the use of tight bands across the lower forehead helpful, likely providing a sensory trick to maintain the eyes open. Other physical devices include tight glasses, glasses with a palpebral splint, and use of dark glasses to help with the light-induced blepharospasm. Oral medications that can be helpful in focal dystonias include GABA-A (benzodiazepines) and GABA-B (baclofen) drugs, as well as anti-cholinergic ones. Clonazepam is a commonly used drug. The benefit of oral medication tends to be limited by their side effects, producing mostly cognitive and behavioral changes, including severe somnolence. Sometimes a combination of multiple drugs at relatively high doses can be a successful option but may take a long time to escalate to the therapeutic doses. A levodopa trial is usually recommended in focal and generalized dystonias that could be caused by dopamine responsive dystonias. Tetrabenazine (a dopamine depletor) and clozapine (a D4 dopamine receptor blocker) have been reported to help tardive dystonias including blepharospasm.

Facial nerve lysis and orbicularis myotomies were once used extensively but have been replaced by chemodenervation. Orbicularis oculi myotomy has been used for patients with blepharospasm with mixed results. Although many patients see an improvement of their condition in the postoperative period, the dystonia seems to overcome the myotomy and symptoms recur over the years. Side effects and complications from these interventions include leftover scars, ectropion, exposure keratitis, and facial asymmetry. Deep brain stimulation has been increasingly used for patients with blepharospasm that have failed other treatment options, or have become resistant to chemodenervation. This option seems particularly useful in severe tardive blepharospasm and in primary generalized dystonias.

Transcranial magnetic stimulation, botulinum toxin cream used topically, Zinc supplementation, mexiletine, and topical acetyl hexapeptide-8 are some of the other treatment options that are under investigation.

Overview on botulinum toxins

BoNT are produced by the bacteria *Clostridium botulinum* and are the most potent toxins known to humans. They cause flaccid paralysis by blocking the release of acetylcholine at the neuromuscular junction [Pellizzari *et al.* 1999]. There are

seven different serotypes that are termed A through G. Only types A and B have been developed for commercial use. The serotypes have a common 150 kDa structure composed of a heavy chain and a light chain linked by a disulfide bond [Pellizzari *et al.* 1999]. The light chain is the active domain, while the heavy chain contains the translocation and receptor binding domains.

BoNT bind to receptors on the neuronal surface through the receptor binding domain which triggers internalization into neuron vesicles via endocytosis. The low pH within the vesicle allows cleavage of the disulfide bond and release of the active light chain which is translocated into the neuronal cytosol. The light chains are metalloproteases which cleave SNARE (soluble N-ethyl-maleimide-sensitive factor attachment protein receptor) proteins on the presynaptic acetylcholine-carrying vesicles, which inhibits vesicular fusion with the cell membrane and therefore blocks exocytosis and release of the acetylcholine [Montecucco and Schiavo, 1994]. The different serotypes act on different SNARE proteins. Serotypes A and E cleave SNAP-25; B, D, F, and G cleave VAMP-2; and C cleaves both SNAP-25 and syntaxin 1a [Montecucco and Schiavo, 1994]. BoNT intoxication is not lethal to the neuron. The effect of the BoNT remains until the SNARE proteins are regenerated. This varies according to the dose and serotype. BoNT type A (BoNT/A) is the longest acting [Rossetto *et al.* 2013].

There are six formulations of BoNT commercially available, including five type A formulations and one type B formulation. These formulations are not interchangeable. Different manufacturing and purification processes are used, yielding different potencies [Carruthers and Carruthers, 2007]. There is no universally accepted method of determining dose equivalency between the different formulations. The FDA assigned specific names to these formulations in 2009. Botox® (onabotulinumtoxinA, Allergan, Inc., US), Dysport® (abobotulinumtoxinA, Ipsen, France), and Xeomin® (incobotulinumtoxinA, Merz Pharmaceuticals, Germany) are type A formulations that are available in the US. Botox® was the first BoNT/A product, and it has been approved for the most indications. In the US, these indications include the treatment of blepharospasm, cervical dystonia, hyperhidrosis, glabellar lines, chronic migraine, upper limb spasticity, and neurogenic detrusor overactivity. As a result, it is the most commonly used BoNT/A. Dysport® is approved in the US for the treatment of cervical dystonia and glabellar

lines. It has been linked to a higher incidence of dysphagia than Botox® [Sampaio *et al.* 2004], although again dose equivalence makes it hard to make unquestionable comparisons. Xeomin® is uniquely free of any complexing proteins and contains less inactivated toxin which is hoped to increase efficacy and decrease development of neutralizing antibodies [Dressler, 2012], although long-term data are not yet available. Its approved indications include blepharospasm, cervical dystonia, and glabellar lines. Neurontox® (Medy-Tox Inc., South Korea) and Lantox® (Lanzhou Biological Products, China) are type A formulations that are not available in the US but are used in other countries. An additional type A formulation, PurTox® (Mentor Worldwide LLC, US) has completed stage III clinical trials [Walker and Dayan, 2014]. MyoBloc® (rimabotulinumtoxinB, Solstice neurosciences, US) is the only commercially available type B formulation. It has been approved for use in treating cervical dystonia.

The type A toxins are in crystallized form and have to be reconstituted with normal saline. Myobloc® is available in solution which is acidic and causes more painful injections [Walker and Dayan, 2014]. It might cause more dry mouth and constipation than type A toxins [Tintner *et al.* 2005]. Xeomin® is the only formulation that is stable at room temperatures. The remaining formulations require refrigeration.

Usually patients that receive BoNT injections can expect long-term efficacy. Loss of effectiveness is rare, and is thought to be due to the formation of neutralizing antibodies in some patients [Greene *et al.* 1994]. Factors contributing to the development of these antibodies include more frequent and higher doses as well as the use of booster injections 2–3 weeks after initial injection. The formulation of Botox® was changed in 1997 to reduce the protein content to help reduce the formation of neutralizing antibodies. The host response to the neurotoxin-associated proteins might play an important role in local and systemic side effects, and the presence of these proteins seems to modulate the immune response [Wang *et al.* 2014]. As mentioned above, Xeomin®'s lack of complexing proteins is thought to make it less likely to cause neutralizing antibodies [Kanovsky *et al.* 2011].

Review of the evidence

The efficacy and favorable side-effects profile of chemodenervation have made it the treatment of

choice for blepharospasm. The expected response rate to BoNT is very high. In a retrospective study, sustained benefit at 2 years was seen in up to 92% of the patients [Hsiung *et al.* 2002]. A recent, comprehensive, evidence-based review by Hallett and colleagues found three class I trials [Jankovic *et al.* 2011; Roggenkamper *et al.* 2006; Wabbels *et al.* 2011], four class II trials [Girlanda *et al.* 1996; Jankovic and Orman, 1987; Nussgens and Roggenkamper, 1997; Truong *et al.* 2008], and one class III trial [Sampaio *et al.* 1997] that fulfilled their criteria, with a total of 866 patients [Hallett *et al.* 2013].

Currently in the US, the only approved BoNT products for use in blepharospasm are incobotulinumtoxinA and onabotulinumtoxinA. We will also discuss abobotulinumtoxinA as this is approved in Europe for blepharospasm. We will review some data on rimabotulinumtoxinB as this is the only B toxin available. The literature on the use of BoNT for blepharospasm is extensive, and therefore we were constrained to choose some of the representative studies for discussion.

AbobotulinumtoxinA (Dysport)

Sampaio and colleagues reported in 1997 the DYSBOT study, a single-blind, randomized parallel study comparing abobotulinumtoxinA *versus* onabotulinumtoxinA, assuming a dosing ratio of 4:1 [Sampaio *et al.* 1997]. This study included 91 patients with either hemifacial spasm or blepharospasm, and showed equivalence in clinical and safety outcomes. Limitations of this study included the small number of patients and the single-blindness. Then, in 2008 the US phase II Dysport blepharospasm study was reported. This was a large, multicenter, randomized, placebo-controlled study that reviewed efficacy of different abobotulinumtoxinA doses (40, 80, and 120 units per eye) [Truong *et al.* 2008]. The best balance of sustained efficacy and favorable safety profile was provided by 80 units per eye.

IncobotulinumtoxinA (Xeomin)

We discuss below the two class I studies that showed noninferiority of incobotulinumtoxinA in comparison with onabotulinumtoxinA [Roggenkamper *et al.* 2006; Wabbels *et al.* 2011].

The 2011 study by Jankovic and colleagues provided evidence for the use of incobotulinumtoxinA for blepharospasm [Jankovic *et al.* 2011].

This was a randomized, placebo-controlled, double-blind trial of efficacy and safety comparing incobotulinumtoxinA (up to 50 units per eye) to placebo administered in a single treatment session. All patients recruited had documented satisfactory response to two previous treatments with a different type of BoNT A. Adverse events (AEs) were common, and reported in 70.3% of A/inco patients *versus* 58.8% of placebo patients. The most common side effects were eyelid ptosis (18.9% *versus* 5.9%), dry eye (18.9% *versus* 11.8%), and dry mouth (14.9% *versus* 2.9%). This was the US pivotal study and was the sole basis for FDA approval of A/inco for the treatment of blepharospasm. A follow-up, approximately 1-year, longitudinal, open-label extension study of the 102 subjects was reported in 2013 [Truong *et al.* 2013]. The results were consistent with sustained benefit and safety. Interestingly, this was a flexible interval study where patients were receiving doses at intervals between 6 and 20 weeks depending on when the previous injections would wear off. No subject developed neutralizing antibodies and the injection interval had no impact on the incidence of adverse events. It seems, however, that previous exposure to other BoNT-A products could induce antibody-associated therapy failure [Dressler *et al.* 2014].

OnabotulinumtoxinA (Botox)

Based on the 2008 AAN evidence-based recommendations, the authors found two efficacy trials that would fulfil their criteria as class II studies [Simpson *et al.* 2008]. The first study by Jankovic and Orman provided class II evidence for chemodenervation on blepharospasm [Jankovic and Orman, 1987]. This was a double-blind, prospective, crossover trial of 11 patients using onabotulinumtoxinA at 25 units per eye. At that time, knowledge of the implications of using booster injections was not available, and therefore the patients were allowed to receive booster injections as needed. The patients on the treatment arm had significant efficacy lasting a mean of 10 weeks. Limitations of this study included the short duration of follow up, and the small number of patients treated. As part of the approval for onabotulinumtoxinA for blepharospasm, data from an open-label study with 1684 patients was also used. But most of the original approval's evidence was based on the dramatic improvement that patients had, and not on the highly rigorous studies that are conducted nowadays. The second

class II study was by Girlanda and colleagues, and used a within-patient comparative design to evaluate onabotulinumtoxinA, with one eye serving as the control for the patient [Girlanda *et al.* 1996]. The study showed greater reduction in blepharospasm on the A/Ona-treated side, but the sample was small (six patients) and no safety data were included in the publication.

RimabotulinumtoxinB (Myobloc)

Although it seems that the percentage of patients developing resistance to BoNT-A preparations has been decreasing over time, once this occurs the only other chemodenervation choice would be switching to rimabotulinumtoxinB. The experience and level of evidence on BoNT-B is much smaller than that of BoNT-A preparations, likely because the former produces more painful injections. A few small, single-center, open-label, retrospective reports have provided some insight into the use of rimabotulinumtoxinB in blepharospasm, most reporting benefit and tolerable side effects [Colosimo *et al.* 2003; Cardoso, 2003; Barnes *et al.* 2005]. In a single-center, single-injector report of 16 patients, average total dose was 3633 units per session [Dutton *et al.* 2006]. Duration of benefit seemed to be shorter, and spread and occurrence of side effects were greater than with BoNT-A products. However, it is not clear how much of these possible failures are also due to the fact that the patients treated had already failed a different toxin, rendering these patient's data not fully comparable with other studies.

Comparison between toxins

As discussed previously, the different BoNT are made using completely different processes, and their doses are not equivalent. Therefore, their benefit, side effects, and treatment indications are not interchangeable. Comprehensive studies comparing the different toxin subtypes are scant. The differentiating features that affect toxin choice include benefit and its duration, side-effect profile, FDA approval for the particular indication, insurance coverage, and ability to inject more frequently.

OnabotulinumtoxinA and abobotulinumtoxinA have been compared in a few studies with a usual 1:4 dosing ratio, and efficacy has been felt to be similar among the products [Hallett *et al.* 2013; Sampaio *et al.* 1997]. One of these trials used a crossover study design in 212 patients, and there

were no differences on the primary outcome, duration of effect or safety profile [Nussgens and Roggenkamper, 1997]. However, lower-level evidence studies have been pointing out to differences among these two drugs, including possible longer duration of effect for the abobotulinumtoxinA formulation. For example, Bentivoglio and colleagues reported on their single-center study retrospectively review their experience with the two drugs, and found that the mean duration of clinical improvement was higher for abobotulinumtoxinA than onabotulinumtoxinA: 80.1 ± 36.3 and 66.2 ± 39.8 days, respectively ($p < 0.01$) [Bentivoglio *et al.* 2009]. Also, in their efficacy scale, Dysport seemed to be more efficacious. However, side effects occurred in 21.8% of the patients who had received Botox, and in 31.6% of those who had received Dysport ($p < 0.01$). Although studies like this have many limitations including the retrospective nature and the lack of randomization, they are important to review as are a closer reflection of clinical practice.

The original European incobotulinumtoxinA study published in 2006 was an active-comparator study against onabotulinumtoxinA, and showed similar benefits with either drug [Roggenkamper *et al.* 2006]. Another double-blind, randomized, parallel group study compared in 2010 incobotulinumtoxinA with onabotulinumtoxinA with a 1:1 dose equivalence [Wabbels *et al.* 2011]. Symptoms were assessed on the Blepharospasm Disability Index (BSDI), Jankovic Rating Scale (JRS), and Patient Global Assessment (PGA) scale at 4 and 8 weeks. There were no statistically significant differences on the BSDI, PGA, and JRS score between the two groups.

Another study used a split-face technique compared onabotulinumtoxinA with incobotulinumtoxinA for blepharospasm [Saad and Gourdeau, 2014]. This was a prospective, randomized, double-blinded study in 48 patients already treated with onabotulinumtoxinA. Half of the cohort received incobotulinumtoxinA on the right side and onabotulinumtoxinA on the left side of their faces, and the other half received incobotulinumtoxinA on the left and onabotulinumtoxinA on the right. Patients received the same medication to either side of the face for four injections. Mean dose per side was 20 units with a 4.9 SD. There were no differences between the two toxins in neither subjective nor objective measures of benefit and side effects. This study also reveals that the

concomitant use of different types of BoNT might be safe, a piece of information that might have practical implications when trying to use inter-toxin differences to address different indications.

In a small study that might reflect clinical practice (although with some methodological limitations) the authors evaluated patient's preference after switching from onabotulinumtoxinA into incobotulinumtoxinA, and noted that patients who prefer incobotulinumtoxinA over onabotulinumtoxinA had a statistically significant shorter treatment interval. In addition, those who preferred incobotulinumtoxinA thought it was more effective, whereas those patients who preferred onabotulinumtoxinA thought it had a longer duration [Chundury *et al.* 2013]. In blepharospasm patients whose duration of benefit from other toxins is less than 10 weeks, use of incobotulinumtoxinA at a shorter interval could be a consideration [Truong *et al.* 2013].

Evidence-based recommendations

There have been two large evidence-based reviews of the literature on chemodenervation for blepharospasm and other movement disorders, one by the AAN in 2008 and another one in 2013 [Simpson *et al.* 2008; Hallett *et al.* 2013]. The 2008 review recommended that BoNT injections should be considered as a treatment option for blepharospasm (level B) [Simpson *et al.* 2008]. The 2013 review gave a level A recommendation for BoNT-A (inco and ona) and level B recommendation for BoNT-A (abo), and a level U recommendation for BoNT-B (rima).

Safety profile

Long-term efficacy and safety of botulinum toxin injections in dystonia is the rule [Ramirez-Castaneda and Jankovic, 2013]. Adverse effects for periocular injections are relatively common, but usually mild. We have reported the prevalence and type of side effects above. Common problems include dry eyes, blurred vision, tearing, ptosis, and ecchymosis. Ptosis usually results from the toxin spreading into the midline of the eye, affecting the palpebral levator system. To prevent ptosis, it is important to avoid injections in the central part of the upper orbicularis muscle. Avoid injections close to the lower central eyelid to decrease the risk of entropion and lower eyelid sagging.

Distant spreading of toxin effects is one of the most important limiting side effects from the use

of BoNT. This iatrogenic botulism is actually very rare. Moreover, injections for blepharospasm require low doses. On an extensive review of the literature on iatrogenic botulism, patients that received less than 100–200 units (such as those with blepharospasm) seemed to have no problems with distant spreading [Crownier *et al.* 2010].

Future directions

There are a number of ongoing studies that will provide insight on the long-term use of BoNT for blepharospasm, including for example the phase IV XCiDaBLE trial. Preliminary data on the cervical dystonia patients treated with incobotulinumtoxinA has been made available but the blepharospasm data is pending. Similar data from the other BoNT drugs could prove useful.

Studies are needed to identify which toxin subtype might be better for specific indications or patients. Also, data necessary to address the safety of concomitant use of different types of BoNT on the same patient is scant. For example, in a patient with sialorrhea and cervical dystonia, some physicians use preferentially BoNT-B for sialorrhea, but due to the less painful injections, might prefer to use BoNT-A for the cervical dystonia. Therefore, data on the safety of this approach would be important.

Another area that needs to be explored is the comparison of different dosing and injection techniques, so to understand best practices. The best dilution for most BoNT procedures has not been properly identified. Finally, the optimum treatment interval for the different toxin types needs to be established through proper evidence.

Conflict of interest statement

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