Botulinum Neurotoxins as Therapeutics

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Abstract

Since first recognized as the cause of food-borne botulism in the early nineteenth century, botulinum toxin was suggested as a potential treatment for involuntary spasms and movements. Multiple double-blind, placebo-controlled, and open-label studies provided evidence that botulinum toxin is a powerful therapeutic tool in a variety of neurologic and other disorders including ophthalmologic, gastrointestinal, urologic, orthopedic, dermatologic, secretory, painful, and cosmetic disorders. We here review the basic mechanisms of botulinum toxin action at the neuromuscular junction and discuss some of its main clinical applications.

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List of Abbreviations

AAN	American Academy of Neurology
Ach	Acetylcholine
BoNT	Botulinum toxin
CD	Cervical dystonia
CD-PROBE	Cervical Dystonia Patient Registry for the Observation of Botulinum Toxin Type A Efficacy Study
EMG	Electromyography
FDA	Food and Drug Administration
nAChRs	Acetylcholine receptors
OMB	Oromandibular dystonia
PD	Parkinson's disease
PREEMPT	Phase III Research Evaluating Migraine Prophylaxis Therapy
SNARE	Soluble *N*-ethylmaleimide sensitive factor attachment protein receptor
TTA	Therapeutics and Technology Assessment
UBI	Unilateral brow injection
VAMP	Vesicle-associated membrane protein

1 Introduction

Since first recognized in 1817 by Christian Andreas Justinus Kerner as the cause of food-borne botulism, botulinum toxin (BoNT) was suggested as a potential treatment for involuntary spasms and movements. However, it was not until 1973 when Alan Scott, M.D., pediatric ophthalmologist and researcher in San Francisco, demonstrated that BoNT injections into the extraocular muscles improved strabismus in monkeys. The first report of clinical application of BoNT was published in 1984, when it was demonstrated to be safe and effective in the treatment of blepharospasm (Frueh et al. 1984). Subsequent multiple double-blind, placebo-controlled, and open-label studies provided evidence that BoNT was a powerful therapeutic tool in a variety of neurologic and other disorders including ophthalmologic, gastrointestinal, urologic, orthopedic, dermatologic, secretory, painful, and cosmetic disorders (Truong and Jost 2006; Jankovic 2009b; Hallett et al. 2013; Naumann et al. 2013) (Table 1).

We will first review the basic mechanisms of BoNT action at the neuromuscular junction and then discuss some of its main clinical applications.

Table 1 Clinical applications of botulinum toxin

Neurologic disorders
Blepharospasm (lid "apraxia")
Oromandibular–facial–lingual dystonia
Laryngeal dystonia (spasmodic dysphonia)
Cervical dystonia (torticollis)
Limb dystonia
Task-specific dystonia (e.g., writer's cramp)
Other axial/focal/segmental dystonias (primary, secondary)
Hemifacial spasm
Limb, head, voice, jaw tremor
Motor and phonic tics
Palatal myoclonus
Nystagmus and oscillopsia
Myokymia
Spasticity (stroke, cerebral palsy, head injury, multiple sclerosis)
Stuttering
Ophthalmologic disorders
Strabismus
Protective ptosis
Pain disorders
Headaches – chronic migraine especially
Tennis elbow and other sports injuries
Chronic anterior knee pain
Lumbosacral strain and back spasms
Radiculopathy with secondary muscle spasm
Myofascial pain syndromes
Gastrointestinal disorders
Sialorrhea
Spasm of the inferior constrictor of the pharynx (cricopharyngeal muscle)
Achalasia (lower esophageal sphincter spasm)
Obesity (distal stomach)
Spasm of the sphincter of Oddi
Anal fissure
Constipation
Anismus
Genito-urologic disorders
Spastic bladder
Detrusor-sphincter dyssynergia
Overactive bladder
Prostatic hypertrophy
Vaginismus

(*continued*)

Table 1 (continued)

Secretory disorders
Hyperlacrimation
Drooling (sialorrhea)
Hyperhidrosis
Gustatory sweating
Cosmetic
Glabellar wrinkles
Brow furrows
Frown lines
"Crow's feet"
Platysma lines
Facial asymmetry
Acne
Others
Diabetic foot ulcers
Pruritus

2 Mechanism of Action of BoNT

2.1 Different and Unique Properties of Various Serotypes of BoNT

The therapeutic value of BoNT is due to its ability to produce local paralysis when injected into a muscle by preventing the release of acetylcholine (Ach) from the presynaptic nerve terminal, also referred to as chemodenervation. There are seven immunologically distinct BoNTs (A–G), with type A being the most studied and most widely used. Synthesized as single-chain polypeptide (molecular weight of 150 kD), each toxin molecule has relatively little potency until it is cleaved by trypsin or bacterial enzymes into a heavy chain (100 kD) and a light chain (50 kD). BoNT exerts its action in a three-step process that involves binding to the receptor to the presynaptic membrane through its heavy chain, internalization of the whole toxin by endocytosis, and enzymatic action of the light chain after it has been cleaved from the heavy chain. The light chain acts as a zinc-dependent protease that selectively cleaves proteins, known as the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins, which are critical for fusion of intraneuronal presynaptic vesicle with the presynaptic membrane, thus preventing the release of Ach. The SNARE target proteins are different for different immunotypes of BoNT. The light chains of both BoNT-A and BoNT-E cleave SNAP-25, but at different sites. The light chains of BoNT-B, -D, and -F cleave synaptobrevin-2, also known as VAMP (vesicle-associated membrane protein), an integral protein of the synaptic vesicle membrane. BoNT-C cleaves both SNAP-25 and syntaxin, another plasma membrane-associated protein. Only types A and B are used clinically.

Table 2 Available types of BoNT in the USA

Generic name	Brand name(manufacturer)	Target
Onabotulinumtoxin A	Botox® (Allergan, Inc., Irvine, CA, USA) or Prosigne® (China)	SNAP 25
Abobotulinumtoxin A	Dysport® (Beaufour Ipsen, France-UK)	SNAP 25
Incobotulinumtoxin A	Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt, Germany)	SNAP 25
Rimabotulinumtoxin B	Myobloc® (US) (WorldMeds, Louisville, KY, USA) or Neurobloc® (Europe)	VAMP (synaptobrevin)

Legend: *BoNT* botulinum toxin, *SNAP* soluble N-ethylmaleimide-sensitive factor attachment protein receptor, *VAMP* vesicle-associated membrane protein

There is considerable evidence that BoNT injected peripherally also influences central nervous system function. By blocking gamma as well as alpha motor neurons, there is denervation of intrafusal muscle fibers. This reduces muscle spindle afferent input to the central nervous system and thereby modifies sensorimotor and proprioceptive pathways (Giladi 1997; Hallett 2000; Rosales and Dressler 2010). These mechanisms may contribute to the therapeutic effects of BoNT in focal dystonias beyond the effects anticipated on the basis of muscle relaxation alone. There is also evidence that BoNT spreads not only to adjacent muscles but also to muscles on the contralateral side of the body (Frick et al. 2012). This is based on a study in which botulinum toxin (2.5 U) was injected into the tibialis muscle of anesthetized rats ($n = 26$) whereas control animals ($n = 25$) received a saline injection. Neuromuscular function, pharmacology, and expression of acetylcholine receptors (nAChRs) were evaluated in the tibialis at 0, 4, and 16 days after injection on the opposite side and in saline-injected controls. Although the mechanism of spread to the contralateral sides is not clear, the investigators demonstrated a decrease in specific twitch tension on the contralateral side and an increased sensitivity to atracurium on the toxin-injected side, despite upregulation of expression of acetylcholine receptors.

The original commercial preparation of BoNT was onabotulinumtoxin A, marketed as Botox® (Allergan, Inc., Irvine, CA, USA). Other forms of BoNT-A clinically available in the USA are abobotulinumtoxin A or Dysport® (Beaufour Ipsen, France-UK) and incobotulinumtoxin A or Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt, Germany) (Albanese 2011). Another type of BoNT-A currently in clinical trials is PureTox® (Johnson & Johnson, USA). In addition, there is a Chinese form of BoNT-A (Prosigne or CBTX-A, Lanzhou Biological Products Institute, China), a Korean preparation (Meditoxin®/Neuronox®, Medy-Tox, South Korea), and many other formulations in experimental clinical trials and in development (Table 2).

Currently, the only preparation of BoNT-B is rimabotulinumtoxin B, known by the brand name Myobloc® (USA) or Neurobloc® (Europe) (US WorldMeds, Louisville, KY, USA). BoNT-B is an antigenically distinct form of BoNT and has unique physical and clinical properties that distinguish it from BoNT-A (Sadick 2003).

It is important to note that the biologic activity, measured in units, is different for the different products. Each preparation should be considered unique in its potency and properties and is measured with proprietary units that are considered to be non-interchangeable (Albanese 2009, 2011). However, through clinical practice when switching from one to another product, also supported by numerous comparison studies, many clinicians have used the following conversion ratios: Dysport® versus Botox® as 2.5 to 1 (Marchetti et al. 2005) and Myobloc/Neurobloc® versus Botox® as 50:1 (Pathak et al. 2006), whereas Xeomin® and Botox® seem to be equivalent in their potency (Jost et al. 2007; Frevert 2010; Dressler et al. 2011).

In Botox® and Dysport®, the BoNT component is formed by botulinum neurotoxin and by nontoxic proteins known as complexing proteins (Dressler and Benecke 2007), whereas the purification and manufacturing process for Xeomin® removes the complexing proteins (Frevert 2009b) giving it the highest specific neurotoxin activity (Frevert 2010).

2.2 Antigenicity and Immunoresistance

In addition to the biologically active toxin, many products include various amounts of nontoxin proteins like hemagglutinins and other proteins that are not required to stabilize the toxin but can have some immune-stimulating activity (Frevert 2009a). Xeomin® and PureTox® are free of such complexing proteins (Frevert 2009b). Some patients stop responding to BoNT injections after sometimes years of benefit. This seems to be secondary to the production of blocking antibodies directed against the heavy chain of the BoNT molecule (Jankovic and Schwartz 1995). Methods used to detect blocking antibodies include the mouse protection assay, the mouse phrenic nerve hemidiaphragm test, and many other tests (Hanna et al. 1999). The most commonly available test is the Western blot assay, but because of its lack of sensitivity and specificity, this test does not reliably predict true immunoresistance (Hanna and Jankovic 1998). A unilateral brow injection (UBI) is a useful clinical test, as inability to frown on the injected side due to weakness of the procerus and corrugator muscles confirms the absence of clinically meaningful immunoresistance (Hanna et al. 1999). The original preparation of Botox® contained 25 ng of neurotoxin complex protein per 100 U, but in 1997, the Food and Drug Administration (FDA) approved a new preparation that contains only 5 ng per 100 U, which has been associated with lower antigenicity (Jankovic et al. 2003). Depending on the technique used to detect blocking antibodies, the risk of antibodies to Botox® has markedly decreased (Mejia et al. 2005) and is now estimated to be about as low as 1.2 % of patients receiving the product repeatedly for up to 4 years (Brin et al. 2008). BoNT-B may be a useful alternative for patients who develop resistance to BoNT-A (Berman et al. 2005), but this preparation may be associated with higher risk of antigenicity (Jankovic et al. 2006). In one study, the effect of BoNT-B was sustained for up to 2.5 years in type A-resistant patients, but the magnitude of response diminished over time (Factor et al. 2005). Although the various neurotoxins are antigenically different, they contain a common subunit structure, and cross-reactive

epitopes may cause cross-neutralization of antibodies (Atassi et al. 2008). Most patients who develop blocking antibodies to one type of BoNT thus have an increased risk of developing blocking antibodies to a different type of BoNT despite a possible initial good response to the new BoNT. While low antigenicity has been predicted with formulations of BoNT without complexing proteins (e.g., Xeomin® and PureTox®), no long-term data are yet available to support this notion.

Although frequently suggested, an association between a large cumulative dose of BoNT and long treatment duration with the development of anti-BoNT antibodies could not be confirmed (Bakheit et al. 2011).

2.3 Adverse Effects

Most of the adverse effects of BoNT are not preventable, but some are clearly associated with wrong dosage, inappropriate selection of muscles, and faulty injection techniques. Clinicians inexperienced with BoNT treatment should consider referral to a specialist experienced with proper use of BoNT. There are many controversies related to BoNT techniques, including the role of electromyography (EMG) in guiding injections, particularly to reach certain muscles (Comella et al. 1992). Although EMG guidance may be appropriate for BoNT treatment of limb dystonia, this does not mean that placement with EMG guidance correlates with better results, since the selection of the muscle involved in the hand dystonia is based on clinical examination and not on EMG (Jankovic 2001). Two class II methodological studies compared EMG versus muscle stimulation for needle localization; one of these studies showed enhanced accuracy of needle placement under EMG guidance (Molloy et al. 2002) while the other was inconclusive (Geenen et al. 1996). A more recent simple blind randomized control study showed that EMG guidance was associated with slightly better clinical outcome and a lower dose of BoNT in the treatment of cervical dystonia (CD), but the control group had a duration of symptoms twice as long as the EMG-guided group, so the results are difficult to interpret (Werdelin et al. 2011).

Side effects of BoNT injection usually result from an excessive weakness in the injected muscles. Local reactions include pain, edema, erythema, ecchymosis, headache, and short-term hyperesthesia (Lu and Lippitz 2009). The toxin can also diffuse to adjacent muscles and result in unwanted weakness. A number of factors seem to influence diffusion of BoNT including injection technique, concentration, and volume (Ramirez-Castaneda et al. 2013). Rarely, the toxin spreads systemically to distant sites resulting in mild generalized muscle weakness, malaise, nausea, fatigue, rash, or flu-like symptoms (Naumann et al. 2006; Baizabal-Carvallo et al. 2011; Dressler 2010a). It has been proposed that systemic distribution may be mediated by capillary or venous uptake and the volume of fluid used for BoNT reconstitution may increase systematic spread (Crowner et al. 2010).

The most common adverse effects encountered when using BoNT for CD include injection-site pain, muscle weakness, dysphagia, dry mouth, and flu-like symptoms (Poewe et al. 1998; Mejia et al. 2005; Naumann et al. 2006). Flu-like

symptoms occur in 1.7–20 % of BoNT-A injections (Baizabal-Carvallo et al. 2011) without marked differences between various serotypes of formulations although head-to-head comparisons are lacking. This side effect, however, seems to be more frequent with BoNT-B, observed in 5–55 % of injections (Baumann et al. 2003; Baumann et al. 2005a, b). The BoNT-related flu-like symptoms are typically mild, develop within 10 days of the injection, and last an average of 2–3 days, but may last up to 14 days and in rare cases render the patient bedridden. The symptom can be usually relieved with over-the-counter antipyretics and analgesics (Baizabal-Carvallo et al. 2011).

Results of a meta-analysis of 36 randomized controlled studies comprised of 1,425 subjects who received treatment with Botox® for various indications reported a rate of mild-to-moderate adverse effects of approximately 25 % in the Botox®-treated group compared with 15 % in the control group ($p < 0.001$). No severe adverse events, however, have been reported (Naumann and Jankovic 2004). In February 2008 the FDA expressed concern about potential severe adverse effects (respiratory compromise and death) associated with the use of onabotulinumtoxin A, based on submitted reports of children treated for cerebral palsy-associated limb spasticity. According to evidence-based clinical guidelines published by the American Academy of Neurology (AAN) in 2010, BoNT is considered to be an effective treatment for spasticity in children and adolescent with cerebral palsy (Delgado et al. 2010). In the 17 studies they reviewed, the most common adverse effects were localized pain, unsteadiness and increased falls, and fatigue. Although excessive weakness was noted in some cases, no deaths were reported.

The Cervical Dystonia Patient Registry for the Observation of Botulinum Toxin Type A Efficacy Study (CD-PROBE) is an ongoing registry aimed at understanding the use of Botox® in the treatment of CD (Jankovic et al. 2011a). Preliminary results from CD-PROBE suggest that repeated injections of Botox® have a low rate of adverse effects and are associated with meaningful and sustained relief of CD pain and improvement in quality of life (Charles et al. 2010). This has been confirmed by other retrospective series (Camargo et al. 2011), and there are other longitudinal observational studies currently under way designed to provide data on long-term clinical use of BoNT (Fernandez et al. 2013a, b).

Patients with post-polio syndrome and Eaton–Lambert syndrome, however, have been reported to have generalized weakness after local BoNT (Erbguth et al. 1993). Other contraindications to the use of BoNT include myasthenia gravis, motor neuron disease, concurrent use of aminoglycoside antibiotics, and pregnancy, although women, inadvertently injected during pregnancy, reported no untoward side effects to the fetus (Jankovic 2010a).

3 Clinical Application

BoNT is currently used in a wide variety of disorders, a few of which have been approved by the FDA (Table 3) or recommended by medical organizations (Table 4).

Table 3 FDA-approved botulinum toxin products

Trade name	Drug name	FDA-approved indications
Botox®	Onabotulinumtoxin A	Cervical dystonia, severe primary axillary hyperhidrosis, strabismus in patients ≥12 years old, blepharospasm in patients ≥12 years of age. Upper limb spasticity in adult patients. Temporary improvement in the appearance of moderate to severe glabellar lines
Dysport®	Abobotulinumtoxin A	Cervical dystonia, temporary improvement in the appearance of moderate to severe glabellar lines
Xeomin®	Incobotulinumtoxin A	Cervical dystonia, blepharospasm
Myobloc®	Rimabotulinumtoxin B	Cervical dystonia

Table 4 Level of evidence for clinical use of BoNT

Level A (established effective)	Blepharospasm Cervical dystonia Spasticity in adults Equinus varus deformity in children with cerebral palsy Axillar hyperhidrosis Anal fissure Idiopathic detrusor overactivity
Level B (possibly effective)	Hemifacial spasm Adductor laryngeal dystonia Adductor spasticity in children with cerebral palsy Focal upper extremity dystonia Upper extremity essential tremor Palmar hyperhidrosis Pain control in children with cerebral palsy and upper extremity spasticity Allergic rhinitis Sialorrhea.
Level C (probably effective)	Gustatory sweating Oromandibular dystonia Laryngeal dystonia.

3.1 Neurological Disorders

Since the first placebo-controlled trials of BoNT in the treatment of CD (Tsui et al. 1985, 1986) and cranial dystonia, including blepharospasm (Jankovic and Orman 1987), hundreds of other studies have been published confirming the efficacy and safety of BoNT in a variety of movement disorders and other neurologic and non-neurologic disorders.

The Therapeutics and Technology Assessment (TTA) Subcommittee of the American Academy of Neurology, in their 2008 evidence-based review (currently being revised), assigned level A recommendation for the use of

BoNT for the treatment of CD and a level B recommendation for blepharospasm (Simpson et al. 2008a, b). This evidence-based review was recently updated by a panel of experts (Hallett et al. 2013). The panel evaluated published data on the four individual commercially available formulations: abobotulinumtoxinA (A/Abo), onabotulinumtoxinA (A/Ona), incobotulinumtoxinA (A/Inco), and rimabotulinumtoxinB (B/Rima) and made the following recommendations: "For the treatment of blepharospasm, the evidence supported a Level A recommendation for BoNT-A, A/Inco, and A/Ona; a Level B recommendation for A/Abo; and a Level U recommendation for B/Rima. For hemifacial spasm, the evidence supported a Level B recommendation for BoNT-A and A/Ona, a Level C recommendation for A/Abo, and a Level U recommendation for A/Inco and B/Rima. For the treatment of oromandibular dystonia, the evidence supported a Level C recommendation for BoNT-A, A/Abo, and A/Ona, and a Level U recommendation for A/Inco and B/Rima. For the treatment of cervical dystonia, the published evidence supported a Level A recommendation for all four BoNT formulations. For limb dystonia, the available evidence supported a Level B recommendation for both A/Abo and A/Ona, but no published studies were identified for A/Inco or B/Rima, resulting in a Level U recommendation for these two formulations. For adductor laryngeal dystonia, evidence supported a Level C recommendation for the use of A/Ona, but a Level U recommendation was warranted for B/Rima, A/Abo, and A/Inco. For the treatment of focal tics, a Level U recommendation was warranted at this time for all four formulations. For the treatment of tremor, the published evidence supported a level B recommendation for A/Ona, but no published studies were identified for A/Abo, A/Inco, or B/Rima, warranting a Level U recommendation for these three formulations".

3.1.1 Blepharospasm

In 1987, Jankovic and Orman reported the results of a double-blind, placebo-controlled trial of onabotulinumtoxin A (Botox®) in 28 patients with cranial-cervical dystonia, including blepharospasm, oromandibular dystonia, and CD, the results of which were in part used by the FDA to approve Botox® in 1989 as a therapeutic agent in patients with strabismus, blepharospasm, and hemifacial spasm (Jankovic and Orman 1987). Subsequently there have been many other studies confirming the safety and efficacy of BoNT-A in the treatment of blepharospasm (Elston 1987; Mejia et al. 2005; Jankovic 2004; Kenney and Jankovic 2008; Gil Polo et al. 2013). Because of the paucity of double-blind, placebo-controlled trials (Roggenkämper et al. 2006), the TTA Subcommittee of the American Academy of Neurology concluded that there is only level B (probably effective) evidence for the efficacy of BoNT-A for the treatment of blepharospasm (Simpson et al. 2008b). This recommendation will likely be changed to level A as a result of more recent, well-designed, controlled trials with various BoNT products.

The onset of the Botox® effect occurs within 24–72 h, peaks at 2–4 weeks, and lasts 3–6 months (Tan 2005). While about a third of all treatment sessions are followed by some side effects (ptosis, blurring of vision or diplopia, tearing, and local hematoma), only 1–2 % affect patient's functioning, and complications

usually improve spontaneously in less than 3 weeks (Elston 1987; Roggenkämper et al. 2006). The relationship between blepharospasm, BoNT, and occurrence of dry eyes in some patients is not well understood.

In a small prospective, randomized, double-blind study on 21 patients with blepharospasm, Prosigne® was found to have similar efficacy, safety, and tolerability than Botox® with a 1:1 dose equivalence (Quagliato et al. 2010a).

Dysport® has also showed sustained efficacy and favorable safety profile with 80 U/eye (Truong et al. 2008a; Truong 2012). The onset of action occurs within 2 weeks of treatment, peaks at 4–8 weeks, and lasts 10–16 weeks (Odergren et al. 1998). In an early double-blind study in patients with blepharospasm who received one injection of Botox® and one injection of Dysport® in two separate treatment sessions, there was similar efficacy and no significant difference in the duration of the treatment effect between the two preparations, although there were significantly ($p < 0.05$) fewer side effects with Botox® (particularly ptosis; $p < 0.01$) (Nüssgens and Roggenkämper 1997). A more recent study however noted that the mean duration of improvement of blepharospasm was significantly longer for Dysport® (Bentivoglio et al. 2009), but confirmed Dysport® had a higher rate of adverse effects. Finally, another study that evaluated the effect of Botox® after switching from Dysport® showed that Botox® was more effective and had a longer duration of effect than Dysport® (Bihari 2005).

The efficacy and safety of Xeomin® in the treatment of blepharospasm was demonstrated by a prospective, double-blind, placebo-controlled, randomized, multicenter study involving 109 patients (Jankovic et al. 2011b). An open-label extension of that study demonstrated maintained efficacy and good tolerability of Xeomin® at 48 weeks, after an average of five injections (Grafe and Hanschmann 2010; Grafe et al. 2010). In that study, the most commonly reported adverse effects were eyelid ptosis, dry eye, and dry mouth. Xeomin® was found to be clinically non-inferior to Botox® in head-to-head studies (Roggenkämper et al. 2006) (Jankovic 2009a; Wabbels et al. 2011). There is no difference between the two preparations in efficacy, safety profile, onset of action, duration, and waning of effect (Jost et al. 2007; Grafe et al. 2009a). Xeomin® is FDA approved for the treatment of blepharospasm (Barnes et al. 2010).

Myobloc® has also been used successfully in the treatment of blepharospasm, especially in Botox®-resistant patients (Dutton et al. 2006), although double-blind controlled studies in these disorders are lacking (Colosimo et al. 2003). However, side effects are more common than typically expected of BoNT-A, particularly pain on injection, ptosis, dry mouth, and dry eyes (Dutton et al. 2006).

Apraxia of eyelid opening, especially when associated with blepharospasm, seems to improve with injection of the pretarsal orbicularis oculi and injection of the pretarsal portion of the eyelid, or pars ciliaris at the lid margin seems critical for the treatment to be effective in that condition (Inoue and Rogers 2007).

3.1.2 Other Cranial Dystonias

Oromandibular dystonia (OMD) is among the most challenging forms of focal dystonia to treat as it rarely improves with medications (Jankovic and Orman 1988;

Klawans and Tanner 1988; Sankhla et al. 1998). Also, there are no surgical treatments, and BoNT therapy can be complicated by swallowing problems. Clenching, trismus, and bruxism are frequent manifestations of oromandibular dystonia. Although most of the data on BoNT in the management of oromandibular dystonia (OMD) come from open-label studies, these provide compelling evidence on the efficacy of both BoNT-A and BoNT-B in patients with OMD (Wan et al. 2005; Jankovic and Orman 1987; Tan and Jankovic 2000; Laskawi and Rohrbach 2001; Alonso-Navarro et al. 2011). Patients with dystonic jaw closure, treated with injections into the masseter and temporalis muscles, generally respond better than those with jaw-opening dystonia. Although most patients with jaw-opening dystonia benefit from injections into the submentalis muscle complex, some may also require injections into the lateral pterygoid muscles (Evidente and Adler 2010). As with blepharospasm, the improvement is usually noted within the first 5 days and persists for about 3–4 months. Early BoNT treatment of oromandibular dystonia, particularly when associated with trismus and bruxism, may prevent dental and other complications, including the temporomandibular joint syndrome.

Frowning without blepharospasm, as a manifestation of upper facial dystonia, often seen in parkinsonian patients, particularly those with progressive supranuclear palsy, can be also effectively treated with BoNT (Hirota et al. 2008).

3.1.3 Laryngeal Dystonia (Spasmodic Dysphonia)

Several studies have established the efficacy and safety of Botox®, Dysport®, and Myobloc® in the treatment of adductor laryngeal dystonia, produced by involuntary contraction of the thyroarytenoid muscle, and this approach is now considered by most to be the treatment of choice for spasmodic dysphonia (Adler et al. 2004b; Wan et al. 2005; Upile et al. 2009). Adverse effects include transient breathy hypophonia, hoarseness, and rarely dysphagia with aspiration (Wan et al. 2005). This approach usually requires a multidisciplinary team, consisting of an otolaryngologist experienced in laryngeal injections and a neurologist knowledgeable about motor disorders of speech and voice. There are three approaches currently used in the BoNT treatment of spasmodic dysphonia: (1) unilateral EMG-guided injection; (2) bilateral approach, injecting with EMG guidance in each vocal fold; and (3) an injection via indirect laryngoscopy without EMG. Irrespective of the technique, most investigators report about 75–95 % improvement in voice symptoms (Jankovic 2010a). However, when Dysport® is used, it seems that unilateral injections are safer than, and as effective as, bilateral injections (Troung et al. 1991; Upile et al. 2009). BoNT produces less consistent benefits when spasmodic dysphonia is accompanied by voice tremor. As for abductor spasmodic dysphonia, one class III prospective, randomized, crossover treatment study involving 15 patients showed no objective benefit of Botox®, whether injected percutaneously or transnasally into the posterior cricoarytenoid muscle (Bielamowicz et al. 2001). However, anecdotal experience from centers that frequently treat patients with spasmodic dysphonia indicates that BoNT-A is an effective treatment even in the abductor form, although the effects are more consistent in patients with adductor form of spasmodic dysphonia (Evidente and Adler 2010).

3.1.4 Cervical Dystonia (CD)

The introduction of BoNT in the treatment of CD has changed the natural history of this disease in that cervical contractures are now much less frequent than they were prior to BoNT (Ramirez-Castaneda and Jankovic 2013). The efficacy and safety of BoNT in the treatment of CD have been demonstrated in several controlled and open trials (Brashear et al. 1999; Brin et al. 1999; Truong et al. 2005, 2010), and the TTA Subcommittee of the American Academy of Neurology concluded that there is level A (effective) evidence for the efficacy of Botox® for the treatment of CD (Simpson et al. 2008b). The most common treatment-related adverse events of BoNT in CD are mild-to-moderate weakness, dysphagia, dry mouth, neck pain, and injection-site pain.

In one of the first clinical trials to evaluate the efficacy of BoNT for the treatment of CD, treatment with Botox® produced significant improvement including reduction in pain. Side effects were few and no significant systemic adverse reactions were noted (Tsui et al. 1986). These results have since been confirmed in numerous short-term (Brin et al. 1987; Gelb et al. 1989; Greene et al. 1990) and long-term studies (Jankovic and Schwartz 1990; Ramirez-Castaneda and Jankovic 2013).

In a small prospective, randomized, double-blind study on 24 patients with CD, Prosigne® was found to have similar efficacy, safety, and tolerability than Botox® with a 1:1 dose equivalence (Quagliato et al. 2010b).

Dysport® was also shown to be significantly more efficacious than placebo at weeks 4, 8, and 12 in a multicenter, double-blind, randomized, placebo-controlled trial on 80 patients with blurred vision and weakness as the only side effects to occur significantly more often with Dysport® (Truong et al. 2005). These results were confirmed by multiple other randomized, double-blind, placebo-controlled trials (Truong et al. 2008b, 2010; Wissel et al. 2001; Truong and Jost 2006). Dysport® has also been shown to be more effective and better tolerated than trihexyphenidyl in the treatment of CD (Brans et al. 1996).

A recent study that evaluated the safety, efficacy, and duration of effect of Botox® after switching from Dysport® in patients with CD showed that Botox® had more efficacy and a longer duration of effect than Dysport® (Bihari 2005). However, another study showed Dysport® to be more effective than Botox® with higher adverse effects, although none of these required withdrawal of therapy or specific management (Ranoux et al. 2002). Finally, a systematic review showed Dysport® to cause more dysphagia than Botox®, possibly as a result of a greater diffusion (Chapman et al. 2007).

Myobloc® has been shown to be more effective than placebo in both type A-responsive and type A-resistant CD (Brashear et al. 1999; Brin et al. 1999; Lew et al. 1997) and may be an alternative in patients who have developed resistance to BoNT-A (Brin et al. 1999). Botox® and Myobloc® were directly compared at 1:40 dose ratio in 139 patients with CD, with no difference in improvement at 4 weeks following injection, but with more frequent dysphagia and dry mouth with Myobloc® (Comella et al. 2005). Another study on 111 patients with CD randomized to receive either Botox® or Myobloc/Neurobloc® at a dosing ratio of 66.7 showed no significant differences in the efficacy or occurrence of

injection-site pain and dysphagia. Dry mouth however was consistently found to be more frequent with Myobloc/Neurobloc® than with Botox® (Pappert et al. 2008). A report of a 44 % of BoNT-B antibody-induced therapy failure in toxin-naïve CD patients after a relatively short exposure may however limit its use (Dressler and Bigalke 2005).

The risk of immunoresistance seems to be higher with Myobloc® than with Botox®. In a prospective, open-label, multicenter study of 333 BoNT-naïve patients with CD, after a median of 9 of Botox® treatments over a mean of 2.5 years (range: 3.2 months to 4.2 years), only 1.2 % tested positive for blocking antibodies (Brin et al. 2008). In one study of 100 patients with CD followed for 42 months over a mean of 5 (up to 12) visits, a third of the patients who were negative for BoNT-B antibodies at baseline became positive for such antibodies at the last visit (Jankovic et al. 2006). Thus, although BoNT-B offers a useful alternative to patients with immunoresistance to BoNT-A, long-term efficacy is limited by the development of blocking antibodies, probably as a result of the cross-reactivity between the two serotypes.

Xeomin® was shown to be an effective and safe treatment of CD in a double-blind, placebo-controlled study of 233 patients, 39 % of which were BoNT naïve (Comella et al. 2011). It was found to be as effective and safe as Botox® in three different clinical trials totaling 816 patients with a 1:1 dose ratio (Jost et al. 2007) and in several other series (Benecke et al. 2005; Dressler 2009). Xeomin® seems to have similar efficacy and safety among treatment-naïve and previously treated patients (Grafe et al. 2009a, b, c; Fernandez et al. 2013a). Repeated treatments with Xeomin® seem effective and well tolerated (Grafe and Hanschmann 2010; Evidente et al. 2013). The clinical effect of Xeomin® begins within 1 week, peaks at approximately 4–6 weeks, and is sustained for about 110 days (Jost et al. 2007). The most frequently reported adverse effects of Xeomin® are mild dysphagia, neck pain, and muscle weakness (Comella et al. 2011). Xeomin® is FDA approved for the treatment of CD (Barnes et al. 2010).

3.1.5 Writer's Cramp, Other Limb Dystonias, and Axial Dystonia

The treatment of hand dystonia with BoNT is more challenging than the other dystonias, because there are more muscles involved in finely coordinated motor function required in the act of writing, dressing, and in various demanding tasks such as playing musical instruments and sport activities. Several open and double-blind controlled trials have concluded that BoNT injections into selected hand and forearm muscles probably provide the most effective relief in patients with various task-specific and occupational dystonias. BoNT stands as the first-line treatment of choice for the majority of focal dystonias (Albanese et al. 2006; Benecke and Dressler 2007; Albanese et al. 2011) and seems to retain its efficacy a decade after initiation of treatment (Lungu et al. 2011). BoNT has also been used to effectively correct abnormal limb postures seen in other movement disorders such as foot dystonia and striatal hand in Parkinson's disease patients (Giladi et al. 1994; Pacchetti et al. 1995), progressive supranuclear palsy, and corticobasal degeneration (Cordivari et al. 2001; Vanek and Jankovic 2001).

A marked improvement in the severity and disability was achieved with EMG-guided injection of BoNT-A in 93 patients with writer's cramp, whereas primary writing tremor was little improved (Marion et al. 2003). In one study, 69 % of 84 musicians reported improvement with EMG-guided Dysport® injections, but only 36 % reported long-term benefit (Schuele et al. 2005). Dysport® was also shown to be effective in a class I randomized, double-blind, placebo-controlled trial in 40 patients with writers' cramp (Kruisdijk et al. 2007) as well as in a class II study (Contarino et al. 2007). On the other hand, Botox® improved focal hand dystonia in 80 % of patients in a class II double-blind, placebo-controlled, crossover study (Cole et al. 1995), with similar results found in another class II study (Tsui et al. 1993).

BoNT has also been used in the treatment of axial postural abnormalities secondary to axial dystonia, with variable success (Jankovic 2010b). One study reported improvement of six of nine patients with lateral axial dystonia (scoliosis) after EMG-guided injection of 500 U of Dysport® into paraspinal muscles at the level of L2–L5 on the side of the trunk flexion (Bonanni et al. 2007). Another study reported improvement of camptocormia in 9 of 11 patients who received 300–600 U of Botox® into the rectus abdominis (Azher and Jankovic 2005). In contrast, ultrasound-guided injection of the iliopsoas muscle with BoNT is not effective in camptocormia (von Coelln et al. 2008).

3.1.6 Hemifacial Spasm

Hemifacial spasm is defined as a neurologic disorder manifested by involuntary, recurrent twitches of the eyelids and other muscles of only one side of the face (Yaltho and Jankovic 2011). The muscular contractions result from an irritative lesion of the ipsilateral facial nerve, most commonly from compression by a vascular loop. While microvascular decompression of the facial nerve has a high success rate, this surgical treatment is associated with certain risks, such as permanent facial paralysis, deafness, stroke, and even death. Therefore, local injections of BoNT into involved facial muscles offer a useful alternative to surgical therapy. Nearly all patients improve; the complications are minimal and transient, and the approach can be individualized by injecting only those muscles – the contractions of which are most disturbing to the patient. Along with blepharospasm, the FDA approved onabotulinumtoxin A injections for hemifacial spasm in 1989.

The average latency from injection to the onset of benefit is 5.4 days, and the total duration of benefit averages 18.4 weeks. Side effects include facial weakness, lid weakness, ptosis, teary or dry eyes, diplopia, and hematoma. The average duration of improvement in hemifacial spasm, 5 months, is longer than in any of the dystonic disorders, and rare patients have achieved long-lasting remissions. Facial myoclonus associated with Rasmussen encephalitis, similar to hemifacial spasm, but pathophysiologically related to focal cortical seizure, has been also reported to improve with BoNT (Jankovic 2010a).

The frequent use of Botox® and Dysport® in the treatment of hemifacial spasm stems mainly from extensive open-label and clinical experience (Gil Polo et al. 2013)

rather than from controlled trials (Jankovic et al. 1990; Jost and Kohl 2001; Kenney and Jankovic 2008). In one class II prospective, blinded study, Botox® was showed to be safe and effective (Yoshimura et al. 1992).

One study that evaluated the effect of Botox® after switching from Dysport® showed that Botox® was more efficacious in treating hemifacial spasm dystonia or hemifacial spasm and had a longer duration of effect than Dysport® (Bihari 2005). However, a class II single-blind, randomized, parallel-design study comparing Botox® and Dysport® at a dose ratio of 1:4 in 91 patients with hemifacial spasm or blepharospasm showed similar clinical efficacy and tolerability of both products (Sampaio et al. 1997). Xeomin® has been shown to be as effective and as safe as Botox®, with a ratio of 1:1 in 17 patients with hemifacial spasm (Dressler 2009). Prosigne® was found to have similar efficacy, safety, and tolerability than Botox® with 1:1 dose equivalence on 36 patients with hemifacial spasm (Quagliato et al. 2010a).

Myobloc® has also been used successfully in the treatment of hemifacial spasm, although double-blind controlled studies in this disorder are lacking (Colosimo et al. 2003; Trosch et al. 2007).

3.1.7 Tremor

Tremor accompanies dystonia in about half of all dystonic patients, and dystonic tremor improves in some patients treated for focal dystonia with BoNT. Chemodenervation with Botox® may ameliorate not only dystonic tremor but also essential tremor involving the hands, as demonstrated by at least two double-blind, placebo-controlled studies (Jankovic et al. 1996; Brin et al. 2001). When wrist extensor injections are avoided, weakness of finger extensors, noted in the initial studies, can be prevented. BoNT can also be considered for rest tremor associated with Parkinson's disease (PD) when antiparkinsonian treatments fail to insure satisfactory relief (Jankovic and Schwartz 1991; Diamond and Jankovic 2006a, b). In an open-label pilot study, Dysport® injection in the masseters markedly improved jaw tremor in 3 PD patients (Schneider et al. 2006).

However, essential tremor and dystonic tremor seem to respond better to BoNT than rest tremors related to PD, and further studies are needed to demonstrate efficacy of BoNT for the latter and to provide insights on how to improve the treatment protocol (Jankovic 2009b).

Although Botox® is clearly a useful treatment in patients with hand tremor, it has also been found effective in the treatment of voice tremor (Adler et al. 2004a) and head tremor (Pahwa et al. 1995). In a small, randomized, crossover trial of onabotulinumtoxin A in 23 patients with disabling tremor in 33 upper limbs related to MS, there was a significant improvement after active treatment compared with that after placebo at 6 and 12 weeks after injection in the Bain score for tremor, writing, Archimedes spiral drawing, drinking from a cup, and in the 9-hole peg test (Van Der Walt et al. 2012). There was, however, no improvement in the quality of life as measured by the Quality of Life in ET Questionnaire (QUEST). Treatment was complicated by transient weakness, noted in 42.2 % of patients treated with BTX, compared to 6.1 % of patients treated with placebo ($p = 0.0005$).

3.1.8 Tics

Motor and phonic tics associated with Tourette syndrome typically improve with antidopaminergic drugs, but when these drugs do not adequately control the tics or are associated with troublesome side effects, BoNT injections into the affected body parts not only may provide satisfactory control of the tics but also may eliminate the premonitory urge. BoNT treatment is particularly useful in the treatment of focal motor tics and phonic tics, including coprolalia. In a placebo-controlled class II study of 18 patients with simple motor tics (Marras et al. 2001), Botox® treatment was associated with a 39 % reduction in the number of tics per minute within 2 weeks after injection against a 6 % increase in the placebo group ($p = 0.004$). In addition, there was a 0.46 reduction in "urge scores" with BoNT, against a 0.49 increase in the placebo group ($p = 0.02$). This preliminary study, however, lacked the power to show significant differences in other measured variables, such as severity score, tic suppression, pain, and patient global impression. However, it measured the results at 2 weeks, when the full effects of Botox® may have not yet been appreciated, and measured the effect of one treatment only, whereas several adjustments in doses and sites of injections over several treatment visits are usually needed in clinical practice. Another class IV open-label study of 15 patients with simple motor tics showed long-term efficacy of Botox® (Rath et al. 2010), with a permanent remission of the treated tic in three patients at 10 years' follow-up. The premonitory urge was similarly reduced.

3.1.9 Spasticity and Other Hypertonic Disorders

In addition to involuntary movement disorders, BoNT has been used effectively to treat spasticity associated with cerebral palsy, multiple sclerosis, or following stroke.

There is extensive data from clinical trials indicating that Botox® is well tolerated and effective in reducing focal upper limb hypertonia following stroke (Childers et al. 2004; Gordon et al. 2004; Turkel et al. 2006; Elia et al. 2009; Simpson et al. 2009). A meta-analysis of seven multicenter, randomized, double-blind, placebo-controlled, parallel-group trials totaling 544 poststroke patients showed that Botox® decreased poststroke spasticity in upper limb-injected muscles proportionally to the dose of BoNT used. Injected muscles included the flexor carpi ulnaris (FCU), flexor carpi radialis (FCR), flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), and biceps brachii (BB) (Yablon et al. 2011). A multicenter, randomized, double-blind, placebo-controlled study of 120 poststroke patients with lower limb spasticity showed that a onetime Botox® injection yielded significant improvement at 4, 5, and 8 weeks (Kaji et al. 2010). Experienced injectors have recommended the following doses of Botox in the treatment of spasticity: for the lower limb, 3–6 U/kg per muscle; for the upper limb above the elbow, 2–3 U/kg per muscle; and for the upper limb below the elbow and posterior tibialis, 0.5–2 U/kg per muscle (Jankovic 2010a).

A double-blind, placebo-controlled, crossover study also demonstrated improvement in spasticity of thigh adductors in patients with multiple sclerosis after receiving Botox® with subsequent functional gain, specifically easier nursing care, and better comfort when sitting in a wheelchair (Snow et al. 1990).

Dysport® also seems to improve upper limb and, to a lesser extent, lower limb spasticity secondary to stroke (Keam et al. 2011).

Xeomin® was also shown to be effective in reducing poststroke upper limb spasticity in a recent open-label study of 145 patients (Kanovsky et al. 2011).

Based on the review of 11 class I trials for adult upper extremity spasticity, one of them using BoNT-B, and three class I trials for lower limb spasticity, the AAN recommends that BoNT should be offered as a treatment option to reduce muscle tone and improve passive function in adults with spasticity (Simpson et al. 2008a).

Several reviews have assessed the therapeutic effect of BoNT-A, Botox® and Dysport® confounded, for spasticity of the upper or lower limbs secondary to cerebral palsy and the consequent impact on quality of life (Lannin et al. 2006; Naumann et al. 2006; Park and Rha 2006; Coutinho et al. 2011). A meta-analysis of 20 randomized controlled trials of Botox® and/or Dysport® versus placebo or rehabilitation, totaling 882 patients, showed that BoNT-A has a good safety profile during the first months of use, with however more systemic side effects. BoNT-A use was related to respiratory tract infection, bronchitis, pharyngitis, asthma, muscle weakness, urinary incontinence, falls, seizures, fever, and unspecified pain (Albavera-Hernández et al. 2009). Since a dose–response relationship has been observed in the frequency and severity of adverse events of BoNT-A (Naumann et al. 2006), it is possible that children with cerebral palsy have a higher probability of occurrence since they require high doses of toxin relative to their body mass.

In children with cerebral palsy, Botox® (2–8, up to 16 U per kg body weight per muscle) is often found effective when injected in calf muscles to correct equinus deformity and toe walking and in the hamstring muscles to correct crouch and scissor gait, improve sitting and hygiene care, and reduce pain. In a double-blind, controlled study, patients with cerebral palsy receiving 40–80 U of Botox® per muscle experienced a significantly greater improvement in Ashworth score and gait measures than the "low-dose" group (20–40 U per muscle) (Wissel et al. 1999). Multiple studies of Botox® or Dysport® injections into the gastrocnemius showed gait improvement over 1–3 months (Simpson et al. 2008a). One randomized, double-blind, placebo-controlled study injecting Dysport® into the thigh adductors and medial hamstrings of children with adductor spasticity showed significant improvement in knee-to-knee distance as well as adductor muscle tone (Mall et al. 2006). The results of many of the studies are difficult to interpret and compare, because patients with various forms and etiologies of spasticity were enrolled and different methodologies were used to inject and rate the patients. Although some double-blind trials have demonstrated meaningful functional improvement in patients with spasticity, other controlled studies have failed to demonstrate improvement. Many of the published studies suffer methodological problems, particularly in selecting the appropriate outcome measures that may or may not capture the functional goals of the patients. The AAN granted BoNT injections a level A of evidence for the treatment of equinovarus deformity in children with cerebral palsy and a level B for treatment of adductor spasticity and for pain control and in children with cerebral palsy and upper extremity spasticity (Level B) (Simpson et al. 2008a).

Xeomin® was reported useful in treating acquired brain injury-induced upper limb spasticity in a series of 192 patients (Barnes et al. 2010) and lower limb spasticity in one case report (Lippert-Gruner and Svestkova 2011). It has been shown to be as effective and as safe as Botox, with a ratio of 1:1 in a series of 94 patients with spasticity (Dressler 2009).

3.2 Painful Disorders

3.2.1 Headache

No significant difference between Botox® and placebo could be demonstrated in four different studies on patients suffering from episodic migraines, defined as less than 15 days of headache per month (Silberstein et al. 2000; Elkind et al. 2006; Relja et al. 2007; Saper et al. 2007; Naumann et al. 2008). Similarly, out of 4 studies of Botox® for chronic daily headache, none demonstrated a significant effect of Botox® on the primary outcome measure (Mathew et al. 2005). Botox® was also ineffective in treating chronic tension headaches in four randomized, placebo-controlled studies (Naumann et al. 2008). Another study reported that imploding headaches (head seems to be crushed, clamped, or stubbed by external forces) and ocular headaches (eye-popping pain) were more likely to respond to Botox® than exploding headaches (buildup of pressure inside the head) (Jakubowski et al. 2006).

One controlled study demonstrated the effectiveness of fixed-site administration of 100 U of Botox® in the treatment of patients with chronic migraine who specifically did not overuse pain medication (Freitag et al. 2008). However, 150 U of Botox would be needed in patients with chronic migraine and medication overuse (Grazzi, 2013). Chronic migraine is defined as headache occurring $\geq$15 days per month for $\geq$3 months, with headaches occurring on $\geq$8 days being classified as migraine headaches or headaches that respond to migraine-specific medications (Olesen et al. 2006). More recently, pivotal results from the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program involving two double-blinded, placebo-controlled studies established Botox® as a safe, well-tolerated, and effective headache prophylactic treatment for chronic migraine using a combination of fixed-site administration and follow-the-pain approach, at doses ranging from 155 to 195 U administered across seven head and neck muscles every 12 weeks for up to five treatment cycles (Aurora et al. 2010; Blumenfeld et al. 2010; Diener et al. 2010; Dodick et al. 2010). However, these results were not replicated with Dysport® (Chankrachang et al. 2011).

The antinociceptive effect of BoNT in headache was initially thought to be a result of relief of muscle spasms, but in vitro studies have shown that BoNT blocks the peripheral release of pain and inflammatory neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide (Aoki 2003, 2005; Gazerani et al. 2009). Moreover, it has been inferred from animal studies that BoNT-A exerts its antinociceptive effects through retrograde transport and involvement of the central nervous system (Bach-Rojecky and Lacković 2009).

3.2.2 Chronic Knee Pain

In one randomized, double-blind, placebo-controlled, crossover trial on 24 patients with chronic anterior knee pain associated with quadriceps muscle imbalance, one 500 U injection of Dysport® in the vastus lateralis associated with retraining of the vastus medialis provided marked pain improvement compared to placebo. This intervention permitted patients to restore a more balanced knee extensor control during functional activity (Singer et al. 2011).

3.2.3 Painful Limbs/Moving Extremities

The syndrome of painful limbs/moving extremities describes a clinical condition characterized by involuntary toe or finger movement associated with pain in the affected hand/arm or foot/leg. Botox® injections in the involved muscles have been shown to improve pain and movement in some case reports (Singer and Papapetropoulos 2007; Eisa et al. 2008).

3.2.4 Other Pain Syndromes

BoNT-A seems effective in controlling musculoskeletal pain, such as myofascial pain, low back pain, trigeminal neuralgia, and other chronic pain syndromes (Reilich et al. 2004; Sycha et al. 2004; Bhidayasiri and Truong 2005; Bohluli et al. 2011). However, these conditions represent a diverse group, and the results with BoNT-A have not been universally positive (Waseem et al. 2011; Zhang et al. 2011). A recent meta-analysis failed to confirm any significant improvement of neck pain after BoNT-A injection (Langevin et al. 2011a, b).

3.3 Hyperhidrosis

Several well-designed trials have demonstrated efficacy of intradermal injection of Botox® and Dysport® in axillar (Heckmann et al. 2001; Naumann and Lowe 2001; Doft et al. 2011; Dressler and Adib Saberi 2013) and palmar hyperhidrosis (Lowe et al. 2002; Solish et al. 2007; Ito et al. 2011). A within-subject comparison showed similar effectiveness and tolerance but longer duration of action of Dysport® compared to Botox® (Simonetta et al. 2003). Xeomin® has been shown to be as effective and as safe as Botox®, with a ratio of 1:1 in 64 patients with hyperhidrosis (Dressler 2009). This was confirmed by a double-blinded study on 46 patients complaining of axillar hyperhidrosis with injection of Botox® under one arm and Xeomin® under the other (Dressler 2010b).

Myobloc® has also been shown to improve axillary as well as palmar hyperhidrosis (Baumann et al. 2005a, b) and appears to be as effective as Botox® in the treatment of axillary hyperhidrosis at a conversion factor of 20:1, with however more discomfort on injection (Dressler et al. 2002). In a recent within-subject comparison of 10 patients, Myobloc® was significantly more effective and had a longer duration than Botox®, at a conversion ratio of 50:1 (Frasson et al. 2011). Xeomin® has also been used successfully for the treatment of axillar hyperhidrosis (Dressler 2012). The TTA Subcommittee of the AAN concluded that there is level

A evidence for the recommendation that BoNT should be offered as a treatment option for axillary hyperhidrosis and level B for palmar hyperhidrosis (Naumann et al. 2008).

Gustatory sweating is a unique entity characterized by profuse sweating of the face, scalp, and neck during or immediately after ingestion of food or drink (Naumann et al. 1997). It most often occurs as a complication of surgery to the area of the face near the parotid glands (Nolte et al. 2004). The effect of Botox® on gustatory sweating has been evaluated in one class II and three class III studies totaling 131 patients, with an effect lasting up to a year (Naumann et al. 1997; Laccourreye et al. 1999; Eckardt and Kuettner 2003; Nolte et al. 2004). At present available evidence supports a Level C recommendation for BoNT for the treatment of gustatory sweating.

3.4 Gastrointestinal Conditions

3.4.1 Sialorrhea

Several studies, including randomized placebo-controlled trials (Ondo et al. 2004; Lagalla et al. 2006; Jackson et al. 2009), have provided evidence that Botox®, Dysport®, or Myobloc® injections in the parotid glands with or without injection in the submandibular glands may be the treatment of choice for sialorrhea and drooling associated with PD and other disorders with bulbar dysfunction, such as amyotrophic lateral sclerosis, cerebral palsy, posttraumatic encephalopathy, and bilateral strokes (Nóbrega et al. 2007; Santamato et al. 2008; Molloy 2007; Basciani et al. 2011; Chinnapongse et al. 2011; Moller et al. 2011). Ultrasound-guided injection may improve the efficacy of BoNT treatment for sialorrhea (Dogu et al. 2004). Xeomin® has been shown to be as effective and as safe as Botox®, with a ratio of 1:1 in a small series of patients with sialorrhea (Dressler 2009).

An open-label study of 30 children with neurological disorders and sialorrhea showed no difference in efficacy or side effects between BoNT-A and BoNT-B (Wilken et al. 2008). Other studies provided evidence that BoNT-B may be more effective than BoNT-A in treating sialorrhea as dry mouth is significantly more frequently noted in patients treated for CD with BoNT-B as compared to BoNT-A (Tintner et al. 2005; Jankovic 2009b; Guidubaldi et al. 2011). However, a recent randomized double-blind crossover trial demonstrated similar efficacy but shorter latency and lower cost of Myobloc® compared to Dysport® (Guidubaldi et al. 2011).

The potential adverse effects of using BoNT for sialorrhea include transient dysphagia and xerostomia although dysphagia has not been reported in any study. In fact, a study of oropharyngeal swallowing dynamics, based on swallowing videofluoroscopy, showed no difference before or 30 days after injections of BoNT-A into the parotids in patients with PD (Nóbrega et al. 2009).

3.4.2 Achalasia

Achalasia is manifested by spontaneous and repetitive contractions of the proximal esophagus with failure of the lower esophageal sphincter to relax during swallowing. This leads to dysphagia. Several small studies have demonstrated the beneficial effects of Botox® injections into the lower esophageal sphincter in the treatment of

achalasia, particularly in patients who are not candidates for surgery or balloon dilatation (Pohl and Tutuian 2007; Barnes et al. 2011; Lakhtakia et al. 2011).

3.4.3 Constipation and Fecal Incontinence

Anismus (constipation due to functional obstruction at the pelvic outlet by paradoxical contraction of the striated sphincter muscles during defecation straining) has been suggested to represent a form of focal dystonia and has been considered as a possible etiology of constipation in some patients (Mathers et al. 1988). Several small open-label studies demonstrated the beneficial effects of Botox® anal injections in the treatment of the subtype of constipation secondary to anismus (Albanese et al. 2003; Cadeddu et al. 2005; Hompes et al. 2012). The puborectalis muscle is usually injected under transrectal ultrasonographic guidance.

On the other hand, rectal hypercontractility can lead to fecal incontinence. Intrarectal Dysport® injections have shown some improvements in fecal incontinence in a small series (Bridoux et al. 2011).

3.4.4 Anal Fissure

Botox® and Dysport® injections into the internal anal sphincter seem effective in treating chronic anal fissure with a low rate of transient incontinence secondary to diffusion to the external anal sphincter and without permanent complications. However, the therapeutic response is heterogenous (Brisinda et al. 2002; Maria et al. 2000; Yiannakopoulou 2012).

3.5 Overactive Bladder and Other Urologic Problems

An increasing number of reports provide evidence that Botox® injections into the bladder wall is an effective treatment in increasing the bladder capacity and improving urge and incontinence in patients with overactive bladder associated with neurogenic and idiopathic detrusor overactivity (Patel et al. 2006; Chen and Liao 2011; Deffontaines-Rufin et al. 2011). However, the rate of treatment discontinuation may be as high as 61.3 % at 3 years, secondary the need to intermittent self-catheterization or urinary tract infections (Mohee et al. 2013). A randomized controlled trial comparing anticholinergic versus BoNT for urinary urge incontinence has recently started (Visco et al. 2012). The TTA Subcommittee of the AAN concluded that there is level A evidence for the recommendation that BoNT should be offered as a treatment option for this urinary disorder (Naumann et al. 2008).

Other genitourinary indications for Botox® treatment include voiding dysfunction due to benign prostatic hypertrophy (Chuang and Chancellor 2006; Marchal et al. 2011).

3.6 Allergic Rhinitis

Two class II placebo-controlled studies with a total of 73 patients demonstrated the efficacy of 20–30 units of Botox® in each nasal cavity to manage the symptoms of

allergic rhinitis (Unal et al. 2003; Yang et al. 2008). Botox® was also superior when compared to intranasal triamcinolone (Yang et al. 2008). However, the follow-up was only for 8 weeks, so the durability of effectiveness is unclear.

3.7 Cosmetic

It is beyond the scope of this review to discuss the vast literature on cosmetic use of BoNT, which represents about half of all the uses of BoNT. Botox® and Myobloc® have been used in brow lifts and for treating glabellar lines, horizontal forehead lines, crow's feet, hypertrophic orbicularis, upper nasalis (bunny) lines, repeated nasal flares, melomental folds, perioral rhytides or smoker's lines, mouth frown, peau d'orange skin, mental crease, facial asymmetry with both hyper- and hypofunctional muscle imbalance, necklace lines, and platysmal bands (Glogau 2002; Baumann et al. 2003; Choi et al. 2013a, b; Dessy et al. 2011). Overly aggressive or imprecise treatment in the cervical area can lead to incompetent mouth, weakness of the neck flexors, and dysphagia (Klein 2001). The duration of effect of BoNT for cosmetic indications ranges from 3 to 4 months and up to 6–8 months, depending on the treatment site and injection technique (Carruthers and Carruthers 2001). Myobloc® seems to have a faster onset of action by 1–2 days for all these muscle groups, but a shorter duration and lesser potency of action when compared to Botox® at a conversion factor of 1:20 to 1:100. In addition, intradermal injections with Myobloc® are more painful than with Botox® (Yamauchi and Lowe 2004).

Botox® injected peri-nasally at a dose of 20–25 units for facial tics also improved acne in two patients despite previous failure of several anti-acne agents. Clearing of peri-nasal acne began 1–2 weeks after each treatment and lasted 4–5 months (Diamond and Jankovic 2006a, b). Xeomin® and Dysport® have recently demonstrated efficacy in the treatment of crow's feet (Prager et al. 2011).

4 Conclusion

Since first recognized as the cause of food-borne botulism in the early nineteenth century, BoNT was suggested as a potential treatment for involuntary spasms and movements. Almost 200 years later, its known clinical applications span across numerous neurological and other diseases. The Neurotoxin Institute was established in 2002 as an umbrella organization providing unbiased educational programs and other information about the broad use of BoNT in different specialties (www.neurotoxininstitute.com).

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