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REVIEW ARTICLE

Therapeutic applications of botulinum neurotoxins in head and neck disorders



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Botox;
Temporomandibular disorder;
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Facial pain

Abstract *Objective:* The aim of this article is to review the mechanism of action, physiological effects, and therapeutic applications of botulinum neurotoxins in the head and neck area.

Study design: An extensive literature search was performed using keywords. The resulting articles were analyzed for relevance in four areas: overview on botulinum neurotoxins, the role of botulinum neurotoxins in the management of salivary secretory disorders, the role of botulinum neurotoxins in the management of facial pain, and the role of botulinum neurotoxins in head and neck movement disorders. Institutional review board approval was not needed due to the nature of the study.

Results: Botulinum neurotoxin therapy was demonstrated to be a valuable alternative to conventional medical therapy for many conditions affecting the head and neck area in terms of morbidity, mortality, and patient satisfaction with treatment outcomes.

Conclusion: Botulinum neurotoxin therapy provides viable alternatives to traditional treatment modalities for some conditions affecting the head and neck region that have neurological components. This therapy can overcome some of the morbidities associated with conventional therapy.

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More research is needed to determine the ideal doses of botulinum neurotoxin to treat different diseases affecting the head and neck regions.

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1. Overview on botulinum neurotoxins

The discovery of botulinum neurotoxin (BTX) in the late 19th century by Van Ermengem was a medical breakthrough, as it unlocked the secret of a deadly disease at that time—botulism. Van Ermengem’s publication in 1897 established the foundation for research on botulism that led to the food preservation measures we use today (Gunn, 1979; van Ermengem, 1979; Erbguth and Naumann, 1999; Scott, 2004). Interest in BTXs increased rapidly in the 20th century in response to the threat of biologic weapons during World War II when American scientists were able to purify BTXs for military use. In the aftermath of World War II, BTXs were employed in the experimental medical field. In 1973, Scott et al. (1973) performed pioneering animal experiments involving the injection of BTX into primate extraocular muscles, and they reported the ability to safely paralyze a given muscle. In 1977, human trials demonstrated that injections of BTX into the extraocular muscle could be an effective treatment for strabismus. As a result of this research, the US Food and Drug Administration (FDA) approved the use of BTX in 1989. In 2004, the FDA released a draft reviewing the approved applications of BTXs, which included strabismus, cervical dystonia, primary axillary hyperhidrosis, and blepharo-spasm (Scott, 1980; Neuenschwander et al., 2000; Blitzer and Sulica, 2001).

BTX is a polypeptide protoxin synthesized by *Clostridium botulinum*, which is a Gram-positive, obligate anaerobic bacterium. *C. botulinum* is classified immunologically into the following distinct serotypes: A, B, C1, C2, D, E, F, and G. BTX is synthesized as a single chain with a molecular weight of approximately 150 kD (Setler, 2002; Thakker and Rubin, 2004). The final weight of these multimeric complexes range from 700 kD for BTX type B to 900 kD for BTX type A, largely reflecting the weight of added surface proteins (Simpson, 1979; Gonnering, 1993).

BTX interferes with the function of the neuromuscular junction (NMJ) by inhibiting the release of acetylcholine from presynaptic terminals. This process begins with the binding of BTX to presynaptic receptors via the heavy chain

molecule followed by internalization of the toxin through receptor-mediated endocytosis. Next, the light chain molecule passes through the vesicle wall. Subsequently, BTX cleaves a protein called SNAP-25, which is essential for the docking and release of acetylcholine from vesicles within nerve endings, hence inhibiting its release outside the cell (Fig. 1). This mechanism explains how an intramuscular injection of BTX produces partial chemical denervation of the muscle, resulting in a localized reduction in muscle activity or “paralysis” (Simpson, 1979; Gonnering, 1993; Neuenschwander et al., 2000; Blitzer and Sulica, 2001; Lam, 2003). Onset of paralysis occurs as rapidly as 6 h after administration, whereas clinical effects are apparent within 24–72 h (Carruthers et al., 2003).

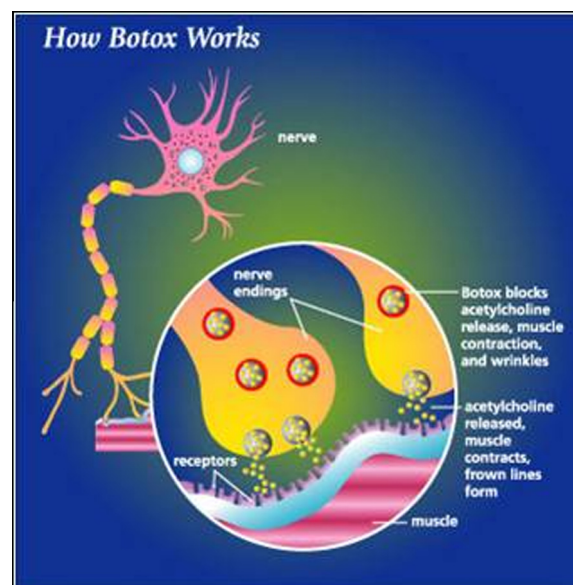


Figure 1 This illustration demonstrates the mechanism by which Botulinum Toxin interfere with the neuromuscular junction. (Source: www.carolinafacialplasticsurgery.com)

The recovery phase is a multistage biologic event that attempts to overcome botulinum blockade of the NMJ. Recovery may be a response to a growth factor secreted by the paralyzed muscle accessory terminals, which “sprout” from the poisoned presynaptic axon and stimulate the development of new NMJs. The primary nerve terminal recovers its full activity and reestablishes itself as the only functioning NMJ by 90 days after BTX administration. However, with repeated exposure to BTX, this process becomes progressively longer.

Each vial of Botox contains 100 units (U) of *C. botulinum* type A neurotoxin complex, 0.5 mg of albumin (human), and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without preservatives. One unit of Botox corresponds to the calculated median intraperitoneal lethal dose required to kill 50% (LD50) of a group of 18–20 g female Swiss-Webster mice. Commercial preparations of BTX available in the United States include Botox (BTX type A, Allergan, Irvine, USA), Myobloc (BTX type B, Solstice Neurosciences, Inc., San Francisco, USA), and Dysport (BTX type A, Ipsen Ltd., Maidenhead, UK). In humans, the LD50 is estimated to be 40 U/kg (2800 U for a 70 kg adult) (Vartanian and Dayan, 2003).

The preparation of freeze-dried BTX (type A) is stable for 2 y when refrigerated at 2–8 °C. Reconstituted BTX (type A) retains its clinical efficacy for up to 6 weeks when stored at 4 °C, yet the package insert recommends use of the entire vial within 4 h when stored at 2–8 °C. Others have reported that BTX loses its clinical efficiency within 12 h despite refrigeration (Gartlan and Hoffman, 1993). In contrast, BTX (type B) is maintained in a liquid form and does not require reconstitution. It retains its potency for 9 months at room temperature (25 °C) and for 3 y at refrigerated temperatures (2–8 °C) (Lam, 2003).

A complete course of BTX treatment for every site in the head and neck should not require more than 100–125 U of BTX per session. Localized side effects include pain, edema, ecchymosis at the site of the injections, headaches, dry mouth, and mild malaise (Kessler et al., 1999; Lam, 2003). No reports of severe life-threatening complications of BTX injections in the head and neck have been published to date. According to the Working Group on Civilian Biodefense, the estimated human median lethal dose of BTX is 1.3–2.1 ng/kg when injected intravenously or intramuscularly and 10–13 ng/kg when inhaled (Arnon et al., 2001). However, localized adverse consequences including unintended and transient muscle paralysis have been occasionally noted from BTX injections of higher doses (Blitzer and Sulica, 2001; Vartanian and Dayan, 2003). Moreover, approximately 5–10% of patients receiving repetitive high doses of BTX (type A) develop antibotulinum antibodies, which may contribute to resistance (Jankovic, 1994; Naumann et al., 1998). Noncosmetic application of BTX typically requires higher doses, which may lead to unexpected complications (e.g. hoarseness, dry mouth, and dysphagia). One study reported new-onset dysphagia after BTX treatment of cervical dystonia in 33% of the patients (Comella et al., 1992). Although no known drug reverses the action of BTX, the use of 0.5% apraclonidine eye drops (iopidine) has been reported to treat ptosis after BTX therapy of the forehead by activating other muscles involved in maintaining upper eyelid retraction (Scheinfield, 2005). BTX could potentially have drug interactions with medications (e.g., succinylcholine, aminoglycosides, D-penicillamine, and cyclosporin) that alter neuromuscular transmission (Bucknall, 1977; Wang et al., 1984; Kadieva et al., 1992; Lam, 2003).

2. BTXs in the management of salivary secretory disorders

Salivary secretory diseases constitute a true challenge to the treating surgeon. These disorders may result from complications following major salivary gland surgery, oropharyngeal cancer surgery (Ellies et al., 2004), or post-traumatic/iatrogenic salivary sialoceles (Marchese-Ragona et al., 2005; Marchese-Ragona et al., 2006). These diseases also include neurologic drooling or sialorrhea, which are caused by either impaired swallowing after head and neck oncological surgery or radiation (Porta et al., 2001; Capaccio et al., 2004; Arnaud et al., 2006; Capaccio et al., 2007). In these cases, BTX is used to inhibit presynaptic acetylcholine release at the NMJs of salivary glands by cleaving the soluble N-ethyl-maleimide-sensitive factor attachment protein receptors, which are proteins involved in the neuroexocytosis process (Sollner et al., 1993). As a result, parasympathetic-dependent secretory function is depressed, whereas the basal flow rate is maintained by the adrenergic pathway, thus avoiding the risk of xerostomia (Ellies et al., 2004; Capaccio et al., 2008). Only a few clinical studies have been published concerning Botox therapy in this field, and there is a lack of long-term follow-up reports.

Frey's syndrome is named after Lucia Frey, a neurologist at the University of Warsaw, who published a landmark paper on the “syndrome du nerf auriculotemporal” in 1923 (Frey, 1923). Frey's syndrome is characterized by sweating and flushing of the facial skin during meals. The postulated etiology is an aberrant dysregeneration of the sectioned parasympathetic fibers normally innervating the parotid gland. The traumatized fibers lose their parotid targets and regenerate to innervate the vessels and sweat glands of the overlying skin. In order for this aberrant dysregeneration to occur, the sympathetic fibers to these vessels and sweat glands have to be damaged, which is a frequent event in either parotid surgery or penetrating parotid trauma. The regular function of the parotid parasympathetic fibers is to increase salivary secretion during eating. The activation following aberrant regeneration produces an activation of new targets during meals, resulting in local vasodilatation, known as “gustatory flushing,” and localized sweating, known as “gustatory sweating.” This syndrome occurs because both parasympathetic fibers going to the parotid and sympathetic fibers going to the skin and sweat glands join the auriculotemporal nerve, which is within the vicinity of the surgical field (Sato, 1977). In addition, the cholinergic receptors on the sweat glands are muscarinic, predominantly of the M3 subtype, and similar to that of the parasympathetic salivary gland nerves, with acetylcholine as the main neurotransmitter (Matthews and Robinson, 1980; Vilches et al., 1995). The treatment modalities proposed for gustatory sweating can be classified in five main groups: (1) external radiotherapy, (2) local or systemic application of anticholinergic drugs, (3) surgical section of some portion of the efferent neural arc, (4) interposition of a subcutaneous barrier (fat or muscle), and (5) injection of BTX in the involved skin.

The injection of BTX type A in the skin for the treatment of gustatory sweating was proposed in 1995 (Drobik and Laskawi, 1995; Vilches et al., 1995). Although there is not an ideal protocol for using BTX in the treatment of Frey's syndrome, Capaccio et al. (2008) developed a protocol with a good clinical outcome. Each parotid gland receives 25–60 U of Botox per treatment fractionated into 4 doses because the gland is conventionally divided into anterior, posterior, upper,

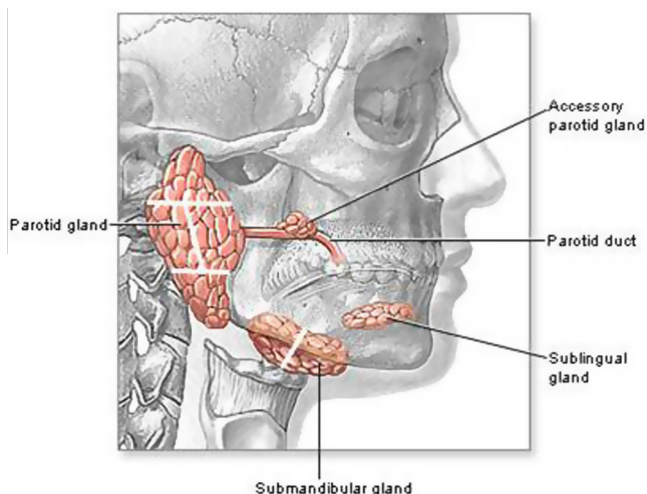


Figure 2 This illustration demonstrates the areas of Botox injection in the major salivary glands. The parotid is divided into four portions each receives 10–15 U of Botox; were as the submandibular gland divided into anterior and posterior halves each receives no more than 10–20 U of Botox.

and lower quadrants, none of which receives more than 15 U of Botox. All injections should be within the body of the gland, and the injections should be performed under ultrasound guidance. In cases of total parotidectomy, the injections should be directed toward the affected skin area.

In cases of salivary secretory disorders associated with hypersalivation or sialorrhea (e.g., neurologic drooling due to Parkinson disease), the above protocol can be implemented, and in addition, the submandibular gland should receive 10–40 U of Botox fractionated into 2 doses of no more than 20 U. These doses should be administered anteriorly and posteriorly within the parenchyma of the gland. The distance between each injection should be about 1 cm, and the expected effect of the drug should last for 4 months (Fig. 2).

3. BTXs in the management of facial pain and migraines

The facial anatomy is fairly complex, and different structures can produce pain, so it is imperative for clinicians to identify the precise source of pain to provide effective management. Treatment of facial pain can be quite frustrating for both clinicians and patients because most of these disorders involve multiple components (e.g., somatic, neurogenic, psychogenic components) that can be resistant to conventional medical or behavioral therapy. The use of Botox therapy for the management of facial pain has gained increasing attention in the few past years (Cheshire et al., 1994; De Andres et al., 2003; Kurtoglu et al., 2008).

It is unclear how BTX functions to decrease pain. There are at least five hypothetical mechanisms through which BTX may alter pain sensation: alterations in levels of muscle nociceptor sensitizers (Hohmann and Herkenham, 1999), diminished γ -motor neuron activity (Donaldson et al., 1998), alterations in acetylcholine levels at autonomic synapses, neuroplastic changes in the central nervous system (Wheeler, 2004), and possible alterations in levels of nonacetylcholine neurotransmitters (Bengtsson et al., 1986).

Temporomandibular disorders (TMD) are a variety of disorders involving the temporomandibular joint, the soft tissue structures within the joint, and the mastication muscles. The most common type of painful TMD is myofascial pain, which is characterized by diffuse pain in the mastication muscles, along with muscle dysfunction and tightness. TMD affects young adults between the ages of 20 and 40 y, and females are affected more frequently than males. Approximately 25–30% of the population will seek medical care for TMD during their lifetimes (Lynch et al., 1994). In the majority of patients with myofascial facial pain, the etiologic factors are muscular spasticity and fatigue secondary to microtrauma from malocclusion, bruxisms, hypermobility, external stressors, and individual psychomotor behaviors (e.g., excessive gum chewing) (Okeson, 1985). Because of its paralyzing effect, BTX therapy is expected to decrease stresses on the TMJ and related tissues and relieve the affected muscular component of TMD.

The technique for therapeutic Botox injections in the treatment of myofascial pain applies the same basic principle as in other applications. The injection is directed into the mass of the offending muscle. The most common muscles patients complain about are the temporalis muscle, masseter muscle, and the lateral pterygoid muscle. In this section, we will discuss the operative technique for injection into these muscles (Table 1). Botox (25 U) is usually administered across the temporalis muscle of one side with 1 cm between the injection sites. The masseter muscle is a very strong rectangular muscle that occupies the lateral aspect of the ramus of the mandible. By creating a line from the corner of the ala of the nose to the tragus of the ear, all injections into the masseter should be below this line to avoid injection into the pterygoid fossa, which could result in unwanted effects. The 20 U of Botox used in the masseter should be distributed along the muscle mass (Fig. 3). The lateral pterygoid muscle is a V-shaped muscle with two distinct heads, which reside in the infratemporal fossa. The first step in the technique for injecting this muscle involves placing the patient in a semi-reclined position with his/her mouth slightly open and the mandible shifted to the opposite side of the intended site of injection. Then the needle is advanced around the tuberosity until it hits the lateral pterygoid plate, and 10 U of Botox is deposited. Next, the needle is redirected superiorly to hit the infratemporal crest of the greater wing of the sphenoid where an additional 10 U of Botox is injected after aspiration (Mendes and Upton, 2009).

Migraine is a debilitating headache disorder that affects approximately 15% of the population and is among the top 20 causes for disability as ranked by the World Health Organization. The clinical diagnosis of migraine is based on the International Classification of Headache Disorders (ICDH-2)

Table 1 Starting doses of Botox injections for masticatory muscles.

Muscle	botox units (U)*
Anterior digastric	10
Lateral pterygoid	15
Masseter	20
Temporalis	25
Medial pterygoid	10

* Doses reflect unilateral treatment.

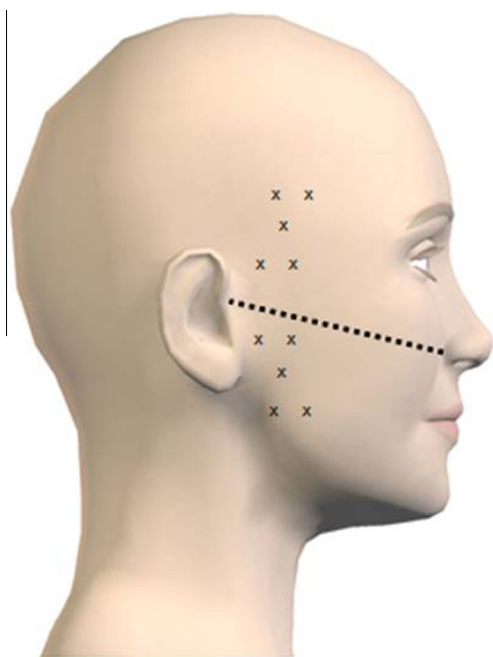


Figure 3 This illustration demonstrates the proposed locations of Botox injection for the temporalis and masseter muscles.

and requires: recurrent headaches (a lifetime history of at least five), untreated or unsuccessfully treated headache with a duration 4–72 h, and at least two of the following pain characteristics: unilateral, pulsating, moderate to severe intensity, and aggravated by routine physical activity. In addition, they are associated with at least one of the following: nausea/vomiting, photophobia, or phonophobia. Moreover, all other forms of headache must be excluded. There are migraines with and without aura, and those with aura account for 80% of migraines. The associated aura can include various reversible visual or sensory symptoms, or it less commonly includes speech or other motor symptoms. Chronic migraine and episodic migraine exist along the spectrum of migraine disorders, but they are distinct clinical entities. Compared to episodic migraine, chronic migraine causes higher levels of individual and social burden because the sufferers are more disabled by their condition and have a reduced quality of life (Katsarava et al., 2012). Episodic migraine sufferers have up to 14 headaches per month, whereas chronic migraine sufferers have 15 or more headaches per month. The possibility of episodic migraine transitioning to chronic migraine is approximately 2.5% per year. On the other hand, chronic migraines become episodic approximately 25% of the time (Bigal et al., 2008; Manack et al., 2011).

BTX type A was approved by the FDA for the treatment of chronic migraines in 2010, and it is the only prophylactic therapy specifically for chronic migraines (Durham and Cady, 2011). The mechanism by which BTX type A reduces migraine frequency and intensity is not completely understood. BTX is thought to inhibit overactive motor neurons and hyperexcitable sensory neurons and suppress peripheral and central sensitization of trigeminal sensory nerves around muscle trigger points. BTX is most effective when injected into an active trigger point or at sites of compression of a branch of the trigeminal nerve. These sites of anatomic compression have

been identified through clinical experience as well as through anatomic dissection. Compression can be related to facial impingement, muscle contraction when there is an intramuscular component to the nerve, as well as blood vessel impingement of the nerve. The supratrochlear and supraorbital nerves run through the corrugator supercilii, and chronic muscle contraction can result in muscle impingement and trigger migraines (Diener et al., 2014; Ashkenazi and Blumenfeld, 2013).

The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials performed an in-depth analysis on injection sites and techniques. Frontal migraines are the most common type of migraines; therefore, injection of 35–40 U BTX in the frontalis, corrugator, and procerus is the most common injection technique. Temporal migraines are the second most common type of migraines, and treatment with 20–25 U BTX per side into multiple trigger points, particularly at the anterior aspect, is recommended. The back of the neck is frequently reported to be a focus of pain. To treat the splenius capitis and semispinalis muscles, they are injected with 20–30 U BTX, but identification of these specific muscles is not feasible. Therefore, the best method of injection is in the upper neck (cervical paraspinal muscles) at the base of the skull 1.5 cm inferior and lateral to the occipital protuberance. The occipitalis is another site of initiation of migraines, and can be treated with injection of 10–20 U BTX on both sides of and just superior to the occipital protuberance (Aurora et al., 2010; Diener et al., 2014).

Trigeminal neuralgia is an excruciating, debilitating orofacial illness, also known as tic douloureux, owing to the facial expression or flinch that often accompanies the painful episode. It is a rare disorder, with an overall incidence of 3–5 persons per 100,000 (with an increased risk in the elderly where the incidence increases two to threefold to 6–12 persons per 100,000) (Katusic et al., 1990). The pain is described as stabbing, shooting, electric shock-like pain lasting seconds to minutes (Table 2). Most times the patient is aware of the trigger of the pain, such as a light touch to an intra- or extraoral region, or a facial or tongue movement. The pain is almost always unilateral and occurs nearly equally in the maxillary and mandibular trigeminal divisions, and less commonly in the ophthalmic division (Katusic et al., 1991; MacDonald et al., 2000). Treatment modalities for trigeminal neuralgia can be divided into pharmacological (e.g., carbamazepine, baclofen, and pimozide) and surgical (e.g., glycerol rhizotomy, microvascular decompression, and stereotactic radiosurgery). Surgical treatment should be considered only when pharmacotherapy fails. Although some surgeons believe that there is a risk of the patient developing more refractory or atypical trigeminal neuralgia if definitive intervention is excessively delayed, medical options should be exhausted prior to surgical intervention (Bowsher et al., 1997; Zakrzewska and Patsalos, 2002). The aim of BTX injections in these cases is to paralyze the trigger points. A recent review by Manolopoulos et al. (2008) demonstrated the efficacy of Botox injections when compared to local anesthesia injections. Two randomized clinical trials showed that BTX type A injections were as efficient as topical anesthetics (bupivacaine 0.5%, lidocaine 0.5%) in terms of the duration and magnitude of pain relief, function, and quality of life, but BTX was less cost effective (Graboski et al., 2005; Kamanli et al., 2005). However, two Cochrane reviews did not provide conclusive evidence that BTX

Table 2 International Headache Society Diagnostic Criteria for Trigeminal Neuralgia.*Description of clinical features*

Unilateral
 Brief electric-shock like pain
 Abrupt onset, abrupt termination (of pain paroxysm)
 Evoked by trivial stimuli, but also occurs spontaneously
 Trigger area
 Remissions

Diagnostic criteria

Paroxysmal attacks of pain lasting from a fraction of a second to 2 min, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C
 Pain has at least one of the following characteristics:
 Intense, sharp, superficial or stabbing
 Precipitated from trigger areas or by trigger factors
 Attacks are stereotyped in the individual patient
 There is no clinically evident neurological deficit
 Not attributed to another disorder

injections are more effective than a placebo when used to treat bilateral benign masseteric hypertrophy and trigger points in myofascial pain syndrome. These results emphasize the need for well-designed, randomized, controlled, clinical trials (Al-Muharraqi et al., 2009; Soares et al., 2012).

Head and neck cancer survivors represent another category of facial pain patients, whether they underwent surgical or radiation treatment.

In 1986, Haubrich (1986) described first-bite syndrome (FBS). Typically, FBS patients report excruciating pain in the parotid region only after the first bite of a meal, hence the name. The pain improves with subsequent masticatory movements during that meal, but invariably returns to the excruciating level at the first bite of the next meal (Chiu et al., 2002). The cause of FBS is largely unknown, but Netterville et al. (1998) proposed that FBS is caused by the loss of sympathetic innervation to the parotid gland with subsequent hypersensitivity of myoepithelial cells to parasympathetic neurotransmitters. This hypersensitivity is thought to elicit a maximal contraction of myoepithelial cells during the first bite of a meal that subsides with continued masticatory action. The concept that pain is elicited ultimately by myoepithelial contraction led to the hypothesis that paralysis of these myoepithelial filaments with BTX may relieve FBS symptoms. In 2008 Ali et al. (2008) reported the first documented use of BTX in the treatment of FBS, thereby adding another application of Botox in the medical field. The operative procedure involves placing the patient in supine position and infiltrating the area some local anesthetic. The area where the patient feels the most intense pain is marked preoperatively. The patient receives an injection of 40–60 U of Botox in the parotid region. It is recommended that the injection be delivered under ultrasound guidance. It may require 24–48 h for the Botox to become effective. The effect of Botox is unpredictable, and when it wears off varies from one individual to another.

4. BTXs in head and neck movement disorders

Head and neck movement disorders encompass a variety of clinical manifestations. This wide spectrum of diseases is a diagnostic enigma for the treating physicians and a socially debilitating illness for the affected individuals. Dyskinesia is

defined as abnormal involuntary movements that primarily affect the extremities, trunk, or jaws and occur as a manifestation of an underlying disease process. Dyskinesia is also a relatively common manifestation of basal ganglia diseases. In contrast, dystonia is defined as a persistent attitude or posture due to contraction of agonist and antagonist muscles of the affected organ or system. Dystonia can be focal, multifocal, or generalized (de Carvalho Aguiar and Ozelius, 2002; Lee, 2007).

Oromandibular dystonia (OD) represents a focal dystonia whereby repetitive or sustained spasms of the masticatory, facial, or lingual muscles result in involuntary and possibly painful jaw movements (Balasubramaniam et al., 2008). The discovery of this condition is attributed to the French neurologist Henry Meige in 1910. Currently OD affects approximately 6.9 in 100,000 persons in the United States. It affects women more commonly than men (2:1), with an average age of onset between 30 and 50 y (Tan and Jankovic, 1999; Blanchet et al., 2005).

The clinical presentation of OD can be quite variable depending on the affected muscles. Chewing, speech, swallowing, and facial expression can be affected in OD, which can cause considerable functional disability. Oral trauma includes rapid wear or early loss of teeth from persistent grinding, and biting of the tongue may occur especially on the affected side (Lee, 2007). Treatment strategies vary and are most effective when focused on treating the etiologic factor. It is classically managed by medication, BTX, local anesthetic blocks, dental appliances, behavioral modification, psychological support, and denervation procedures (Fahn and Jankovic, 1984; Jankovic and Orman, 1987; Goldman and Comella, 2003; Balash and Giladi, 2004). BTX has been shown to be clinically superior to medical therapy, particularly in the treatment of focal dystonias (Dutton, 1996; Tan and Jankovic, 2000). Injection of BTX type A into the muscles of the floor of the mouth, the muscles of mastication, and the extrinsic muscles of the tongue yield great improvement in this subtype of dystonia by paralyzing the hyperactive dysfunctional group of muscles. However, a recent Cochrane review showed no significant difference in pain reduction at four weeks between those who received BTX for subacute and chronic neck pain and those who received placebo injections (Langevin et al., 2011).

5. Conclusions

The potential applications of BTXs extend beyond facial cosmetic surgery. BTX therapy is a superior treatment modality for a number of conditions when compared to pharmacotherapy or surgical intervention in terms of morbidity and mortality. These conditions include salivary secretory disorders, facial pain, and head and neck movement disorders. Although its use seems relatively easy, it is of utmost importance to obtain sound knowledge of the agent, its mechanism of action, the pathophysiology of the disease, and the underlying anatomy before one can incorporate this modality into his or her practice.

Conflict of interest

The authors have no conflict of interest to declare.

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References

- Al-Muharraqi, M.A., Fedorowicz, Z., Al Bareeq, J., Al Bareeq, R., Nasser, M., 2009. Botulinum toxin for masseter hypertrophy. *Cochrane Database Syst. Rev.*(1), CD007510.
- Ali, M.J., Orloff, L.A., Lustig, L.R., Eisele, D.W., 2008. Botulinum toxin in the treatment of first bite syndrome. *Otolaryngol. Head Neck Surg.* 139 (5), 742–743.
- Arnaud, S., Batifol, D., Goudot, P., Yachouh, J., 2006. Nonsurgical management of traumatic injuries of the parotid gland and duct using type a botulinum toxin. *Plast. Reconstr. Surg.* 117 (7), 2426–2430.
- Arnon, S.S., Schechter, R., Inglesby, T.V., Henderson, D.A., Bartlett, J.G., Ascher, M.S., Eitzen, E., Fine, A.D., Hauer, J., Layton, M., Lillibridge, S., Osterholm, M.T., O'Toole, T., Parker, G., Perl, T.M., Russell, P.K., Swerdlow, D.L., Tonat, K., 2001. Botulinum toxin as a biological weapon: medical and public health management. *JAMA* 285 (8), 1059–1070.
- Ashkenazi, A., Blumenfeld, A., 2013. onabotulinumtoxin A for the treatment of headache. *Headache* 53, 54–61, Suppl 2.
- Aurora, S.K., Dodick, D.W., Turkel, C.C., DeGryse, R.E., Silberstein, S.D., Lipton, R.B., Diener, H.C., Brin, M.F., 2010. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PRE-EMPT 1 trial. *Cephalalgia* 30 (7), 793–803.
- Balash, Y., Giladi, N., 2004. Efficacy of pharmacological treatment of dystonia: evidence-based review including meta-analysis of the effect of botulinum toxin and other cure options. *Eur. J. Neurol.* 11 (6), 361–370.
- Balasubramaniam, R., Rasmussen, J., Carlson, L.W., Van Sickels, J.E., Okeson, J.P., 2008. Oromandibular dystonia revisited: a review and a unique case. *J. Oral Maxillofac. Surg.* 66 (2), 379–386.
- Bengtsson, A., Henriksson, K.G., Larsson, J., 1986. Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia. *Arthritis Rheum.* 29 (7), 817–821.
- Bigal, M.E., Serrano, D., Buse, D., Scher, A., Stewart, W.F., Lipton, R.B., 2008. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 48 (8), 1157–1168.
- Blanchet, P.J., Rompre, P.H., Lavigne, G.J., Lamarche, C., 2005. Oral dyskinesia: a clinical overview. *Int J Prosthodont* 18 (1), 10–19.
- Blitzer, A., Sulica, L., 2001. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngoscope* 111 (2), 218–226.
- Bowsher, D., Miles, J.B., Haggett, C.E., Eldridge, P.R., 1997. Trigeminal neuralgia: a quantitative sensory perception threshold study in patients who had not undergone previous invasive procedures. *J. Neurosurg.* 86 (2), 190–192.
- Bucknall, R.C., 1977. Myasthenia associated with D-penicillamine therapy in rheumatoid arthritis. *Proc R Soc Med* 70 (Suppl. 3), 114–117.
- Capaccio, P., Cuccarini, V., Benicchio, V., Minorati, D., Spadari, F., Ottaviani, F., 2007. Treatment of iatrogenic submandibular sialocele with botulinum toxin. Case report. *Br. J. Oral Maxillofac. Surg.* 45 (5), 415–417.
- Capaccio, P., Paglia, M., Minorati, D., Manzo, R., Ottaviani, F., 2004. Diagnosis and therapeutic management of iatrogenic parotid sialocele. *Ann Otol Rhinol Laryngol* 113 (7), 562–564.
- Capaccio, P., Torretta, S., Osio, M., Minorati, D., Ottaviani, F., Sambataro, G., Nascimbene, C., Pignataro, L., 2008. Botulinum toxin therapy: a tempting tool in the management of salivary secretory disorders. *Am. J. Otolaryngol.* 29 (5), 333–338.
- Carruthers, J.D., Lowe, N.J., Menter, M.A., Gibson, J., Eadie, N., 2003. Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. *Plast. Reconstr. Surg.* 112 (4), 1089–1098.
- Cheshire, W.P., Abashian, S.W., Mann, J.D., 1994. Botulinum toxin in the treatment of myofascial pain syndrome. *Pain* 59 (1), 65–69.
- Chiu, A.G., Cohen, J.I., Burningham, A.R., Andersen, P.E., Davidson, B.J., 2002. First bite syndrome: a complication of surgery involving the parapharyngeal space. *Head Neck* 24 (11), 996–999.
- Comella, C.L., Tanner, C.M., DeFoor-Hill, L., Smith, C., 1992. Dysphagia after botulinum toxin injections for spasmodic torticollis: clinical and radiologic findings. *Neurology* 42 (7), 1307–1310.
- De Andres, J., Cerda-Olmedo, G., Valia, J.C., Monsalve, V., Lopez, A., Minguez, A., 2003. Use of botulinum toxin in the treatment of chronic myofascial pain. *Clin. J. Pain* 19 (4), 269–275.
- de Carvalho Aguiar, P.M., Ozelius, L.J., 2002. Classification and genetics of dystonia. *Lancet Neurol.* 1 (5), 316–325.
- Diener, H.-C., Dodick, D.W., Turkel, C.C., 2014. Pooled analysis of the safety and tolerability of onabotulinumtoxin A in the treatment of chronic migraine. *Eur. J. Neurol.* 21 (6), 851–859.
- Donaldson, C.C., Nelson, D.V., Schulz, R., 1998. Disinhibition in the gamma motoneuron circuitry: a neglected mechanism for understanding myofascial pain syndromes? *Appl. Psychophysiol. Biofeedback* 23 (1), 43–57.
- Drobik, C., Laskawi, R., 1995. Frey's syndrome: treatment with botulinum toxin. *Acta Otolaryngol.* 115 (3), 459–461.
- Durham, P.L., Cady, R., 2011. Insights into the mechanism of onabotulinumtoxinA in chronic migraine. *Headache* 51 (10), 1573–1577.
- Dutton, J.J., 1996. Botulinum-A toxin in the treatment of craniocervical muscle spasms: short- and long-term, local and systemic effects. *Surv. Ophthalmol.* 41 (1), 51–65.
- Ellies, M., Gottstein, U., Rohrbach-Volland, S., Arglebe, C., Laskawi, R., 2004. Reduction of salivary flow with botulinum toxin: extended report on 33 patients with drooling, salivary fistulas, and sialadenitis. *Laryngoscope* 114 (10), 1856–1860.
- Erbguth, F.J., Naumann, M., 1999. Historical aspects of botulinum toxin: Justinus Kerner (1786–1862) and the “sausage poison”. *Neurology* 53 (8), 1850–1853.
- Fahn, S., Jankovic, J., 1984. Practical management of dystonia. *Neurol. Clin.* 2 (3), 555–569.

- Frey, L., 1923. Le syndrome du nerf auriculo-temporal. *Rev Neurol* 2, 97–104.
- Gartlan, M.G., Hoffman, H.T., 1993. Crystalline preparation of botulinum toxin type A (Botox): degradation in potency with storage. *Otolaryngol. Head Neck Surg.* 108 (2), 135–140.
- Goldman, J.G., Comella, C.L., 2003. Treatment of dystonia. *Clin. Neuropharmacol.* 26 (2), 102–108.
- Gonnering, R.S., 1993. Pharmacology of botulinum toxin. *Int. Ophthalmol. Clin.* 33 (4), 203–226.
- Graboski, C.L., Gray, D.S., Burnham, R.S., 2005. Botulinum toxin A versus bupivacaine trigger point injections for the treatment of myofascial pain syndrome: a randomised double blind crossover study. *Pain* 118 (1–2), 170–175.
- Gunn, R.A., 1979. Botulism: from van Ermengem to the present. A comment. *Rev. Infect. Dis.* 1 (4), 720–721.
- Haubrich, W.S., 1986. The first-bite syndrome. *Henry Ford Hosp. Med. J.* 34 (4), 275–278.
- Hohmann, A.G., Herkenham, M., 1999. Cannabinoid receptors undergo axonal flow in sensory nerves. *Neuroscience* 92 (4), 1171–1175.
- Jankovic, J., 1994. Botulinum toxin in movement disorders. *Curr. Opin. Neurol.* 7 (4), 358–366.
- Jankovic, J., Orman, J., 1987. Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. *Neurology* 37 (4), 616–623.
- Kadieva, V., van Heerden, P.V., Roux, A., Friedman, L., Morrell, D.F., 1992. Neuromuscular blockade and ventilatory failure after cyclosporine. *Can. J. Anaesth.* 39 (4), 402–403.
- Kamanli, A., Kaya, A., Ardicoglu, O., Ozgocmen, S., Zengin, F.O., Bayik, Y., 2005. Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. *Rheumatol. Int.* 25 (8), 604–611.
- Katsarava, Z., Buse, D.C., Manack, A.N., Lipton, R.B., 2012. Defining the differences between episodic migraine and chronic migraine. *Curr. Pain Headache Rep.* 16 (1), 86–92.
- Katusic, S., Beard, C.M., Bergstralh, E., Kurland, L.T., 1990. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. *Ann. Neurol.* 27 (1), 89–95.
- Katusic, S., Williams, D.B., Beard, C.M., Bergstralh, E., Kurland, L.T., 1991. Incidence and clinical features of glossopharyngeal neuralgia, Rochester, Minnesota, 1945–1984. *Neuroepidemiology* 10 (5–6), 266–275.
- Kessler, K.R., Skutta, M., Benecke, R., 1999. Long-term treatment of cervical dystonia with botulinum toxin A: efficacy, safety, and antibody frequency. German Dystonia Study Group. *J. Neurol.* 246 (4), 265–274.
- Kurtoglu, C., Gur, O.H., Kurkcu, M., Sertdemir, Y., Guler-Uysal, F., Uysal, H., 2008. Effect of botulinum toxin-A in myofascial pain patients with or without functional disc displacement. *J. Oral Maxillofac. Surg.* 66 (8), 1644–1651.
- Lam, S.M., 2003. The basic science of botulinum toxin. *Facial Plast. Surg. Clin. North Am.* 11 (4), 431–438.
- Langevin, P., Peloso, P.M., Lowcock, J., Nolan, M., Weber, J., Gross, A., Roberts, J., Goldsmith, C.H., Graham, N., Burnie, S.J., Haines, T., 2011. Botulinum toxin for subacute/chronic neck pain. *Cochrane Database Syst. Rev.*(7), CD008626.
- Lee, K.H., 2007. Oromandibular dystonia. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 104 (4), 491–496.
- Lynch, M.A., Brightman, V.J., Greenberg, M.S., 1994. *Burket's Oral Medicine: Diagnosis and Treatment.* Lippincott, Philadelphia.
- MacDonald, B.K., Cockerell, O.C., Sander, J.W., Shorvon, S.D., 2000. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 123 (Pt 4), 665–676.
- Manack, A., Buse, D.C., Serrano, D., Turkel, C.C., Lipton, R.B., 2011. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. *Neurology* 76 (8), 711–718.
- Manolopoulos, L., Vlastarakos, P.V., Georgiou, L., Giotakis, I., Loizos, A., Nikolopoulos, T.P., 2008. Myofascial pain syndromes in the maxillofacial area: a common but underdiagnosed cause of head and neck pain. *Int. J. Oral Maxillofac. Surg.* 37 (11), 975–984.
- Marchese-Ragona, R., Galzignato, P.F., Marioni, G., Guarda-Nardini, L., Tregnaghi, A., Restivo, D.A., Staffieri, A., 2005. Endoscopic diagnosis of rhino-parotid fistula and successful treatment with botulinum toxin. *Laryngoscope* 115 (11), 2062–2064.
- Marchese-Ragona, R., Marioni, G., Restivo, D.A., Staffieri, A., 2006. The role of botulinum toxin in postparotidectomy fistula treatment. A technical note. *Am. J. Otolaryngol.* 27 (3), 221–224.
- Matthews, B., Robinson, P.P., 1980. The course of post-ganglionic sympathetic fibres distributed with the trigeminal nerve in the cat. *J. Physiol.* 303, 391–401.
- Mendes, R.A., Upton, L.G., 2009. Management of dystonia of the lateral pterygoid muscle with botulinum toxin A. *Br. J. Oral Maxillofac. Surg.* 47 (6), 481–483.
- Naumann, M., Toyka, K.V., Mansouri Taleghani, B., Ahmadpour, J., Reiners, K., Bigalke, H., 1998. Depletion of neutralising antibodies resensitises a secondary non-responder to botulinum A neurotoxin. *J. Neurol. Neurosurg. Psychiatry* 65 (6), 924–927.
- Netterville, J.L., Jackson, C.G., Miller, F.R., Wanamaker, J.R., Glasscock, M.E., 1998. Vagal paraganglioma: a review of 46 patients treated during a 20-year period. *Arch. Otolaryngol. Head Neck Surg.* 124 (10), 1133–1140.
- Neuenschwander, M.C., Pribitkin, E.A., Sataloff, R.T., 2000. Botulinum toxin in otolaryngology: a review of its actions and opportunities for use. *Ear Nose Throat J* 79 (10), 788–789, 792, 794 passim.
- Okeson, J.P., 1985. *Fundamentals of Occlusion and Temporomandibular Disorders.* Mosby, St. Louis.
- Porta, M., Gamba, M., Bertacchi, G., Vaj, P., 2001. Treatment of sialorrhoea with ultrasound guided botulinum toxin type A injection in patients with neurological disorders. *J. Neurol. Neurosurg. Psychiatry* 70 (4), 538–540.
- Sato, K., 1977. The physiology, pharmacology, and biochemistry of the eccrine sweat gland. *Rev. Physiol. Biochem. Pharmacol.* 79, 51–131.
- Scheinfeld, N., 2005. The use of apraclonidine eyedrops to treat ptosis after the administration of botulinum toxin to the upper face. *Dermatol. Online J.* 11 (1), 9.
- Scott, A.B., 1980. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 87 (10), 1044–1049.
- Scott, A. B. (2004). “Development of botulinum toxin therapy”. *Dermatol Clin* 22(2): 131–133, v.
- Scott, A.B., Rosenbaum, A., Collins, C.C., 1973. Pharmacologic weakening of extraocular muscles. *Invest. Ophthalmol.* 12 (12), 924–927.
- Setler, P.E., 2002. Therapeutic use of botulinum toxins: background and history. *Clin. J. Pain* 18 (6 Suppl), S119–124.
- Simpson, L.L., 1979. The action of botulinum toxin. *Rev. Infect. Dis.* 1 (4), 656–662.
- Soares, A., Andriolo, R.B., Atallah, A.N., da Silva, E.M., 2012. Botulinum toxin for myofascial pain syndromes in adults. *Cochrane Database Syst. Rev.* 4, CD007533.
- Sollner, T., Bennett, M.K., Whiteheart, S.W., Scheller, R.H., Rothman, J.E., 1993. A protein assembly-disassembly pathway in vitro that may correspond to sequential steps of synaptic vesicle docking, activation, and fusion. *Cell* 75 (3), 409–418.
- Tan, E.K., Jankovic, J., 1999. Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up. *Neurology* 53 (9), 2102–2107.
- Tan, E.K., Jankovic, J., 2000. Tardive and idiopathic oromandibular dystonia: a clinical comparison. *J. Neurol. Neurosurg. Psychiatry* 68 (2), 186–190.

- Thakker, M.M., Rubin, P.A., 2004. Pharmacology and clinical applications of botulinum toxins A and B. *Int. Ophthalmol. Clin.* 44 (3), 147–163.
- van Ermengem, E., 1979. Classics in infectious diseases. A new anaerobic bacillus and its relation to botulism. E. van Ermengem. Originally published as “Ueber einen neuen anaeroben Bacillus und seine Beziehungen zum Botulismus” in *Zeitschrift für Hygiene und Infektionskrankheiten* 26: 1–56, 1897. *Rev. Infect. Dis.* 1 (4), 701–719.
- Vartanian, A.J., Dayan, S.H., 2003. Complications of botulinum toxin A use in facial rejuvenation. *Facial Plast Surg Clin North Am* 11 (4), 483–492.
- Vilches, J.J., Navarro, X., Verdu, E., 1995. Functional sudomotor responses to cholinergic agonists and antagonists in the mouse. *J. Auton. Nerv. Syst.* 55 (1–2), 105–111.
- Wang, Y.C., Burr, D.H., Korthals, G.J., Sugiyama, H., 1984. Acute toxicity of aminoglycoside antibiotics as an aid in detecting botulism. *Appl. Environ. Microbiol.* 48 (5), 951–955.
- Wheeler, A.H., 2004. Myofascial pain disorders: theory to therapy. *Drugs* 64 (1), 45–62.
- Zakrzewska, J.M., Patsalos, P.N., 2002. Long-term cohort study comparing medical (oxcarbazepine) and surgical management of intractable trigeminal neuralgia. *Pain* 95 (3), 259–266.