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Review article

Mechanism and clinical use of botulinum neurotoxin in head and facial region

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Abstract

Purpose: Botulinum neurotoxin (BoNT) is a biological toxin produced by *Clostridium botulinum*. BoNT is a potent toxin extensively used in therapeutic interventions. This review provides an updated overview of the mechanisms of action and clinical applications of BoNT in head and facial region.

Study selection: MEDLINE/PubMed searches were conducted using the terms "botulinum neurotoxin" and "dentistry" along with a combination of other related terms. In addition, studies were manually selected from reference lists of the selected articles.

Results: The Food and Drug Administration in the United States initially approved BoNT to treat strabismus, blepharospasm, and hemifacial spasms. The use of BoNT in dermatology and cosmetics has been widely established and has created a revolution in these fields. Over the years, its applications in various medical specialties have expanded widely. Owing to its safety, efficacy, and long duration of action, it is well-accepted by patients. BoNT/A and BoNT/B are widely used in clinical practice. Several off-label uses of BoNT in the dental fraternity have yielded promising results. We have elaborated on the speculated mechanism of action, dosage, effective sites of injection, and adverse effects of each therapeutic application. The various clinical indications for BoNT include bruxism, myofascial pain, temporomandibular joint dislocation, hemifacial pain, orofacial dystonia, facial paralysis, chronic migraine, and trigeminal neuralgia.

Conclusions: BoNT is a safe treatment that can be used effectively, provided that the clinician has adequate knowledge regarding the mechanism, injection techniques, and local and systemic side effects and that it is administered cautiously and purposefully.

Keywords: Botulinum neurotoxin, Clinical use, Orofacial, *Clostridium botulinum*

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1. Introduction

Food-borne botulism, derived from the Latin term "botulus," which means "sausage," was first described in the 18th century. The term was used to define a fatal condition characterized by muscular paralysis resulting in respiratory arrest upon the consumption of raw sausages[1]. Botulinum neurotoxins (BoNTs), which cause botulism, are zinc-dependent metalloproteases produced by an anaerobic, spore-forming, Gram-positive bacterium, *Clostridium botulinum*, and are classified into seven serotypes (BoNT/A-G) based on their antigenic properties. Apart from the seven distinct BoNTs, an additional serotype has been reported; however, further validation is required for confirmation[2,3].

Naturally produced BoNTs are non-covalently associated with one or several non-toxic neurotoxin-associated proteins (NAPs) and form high molecular weight (up to ~900 kDa) progenitor toxin complexes (PTCs) at an acidic pH. The PTCs dissociate into BoNTs and NAPs at neutral or alkaline pH. NAPs play a vital role in protecting fragile BoNTs from the harsh environment of the gastrointestinal tract and in facilitating the passage of BoNTs through the intestinal epithelial barrier. BoNT is released from PTCs after absorption from the intestinal epithelial barrier. Free BoNTs are transported to neuromuscular junctions (NMJs) via general circulation, subsequently inhibiting acetylcholine exocytosis and resulting in flaccid paralysis[4]. BoNTs are potent toxins and are currently being extensively researched, not only for their lethality but also for their potential use in therapeutic interventions owing to their safety, efficacy, and long duration of action. BoNT/A and BoNT/B are widely used in clinical practice[5].

In the early 19th century, the first toxin of BoNT (BoNT/A) was identified. Immediately after its discovery, it was widely used for developing biological weapons, given its effects on the nervous system, and it was studied extensively during the Second World War. The therapeutic use of BoNT in the medical field began in the late 19th century[6,7]. Human use of BoNT was first attempted to treat strabismus (crossed eyes) in 1977 by Scott[6]. Since then, many medical practitioners have used BoNT to treat eyelid twitching and muscle spasms[8]. BoNT/A has also been used to treat neurological

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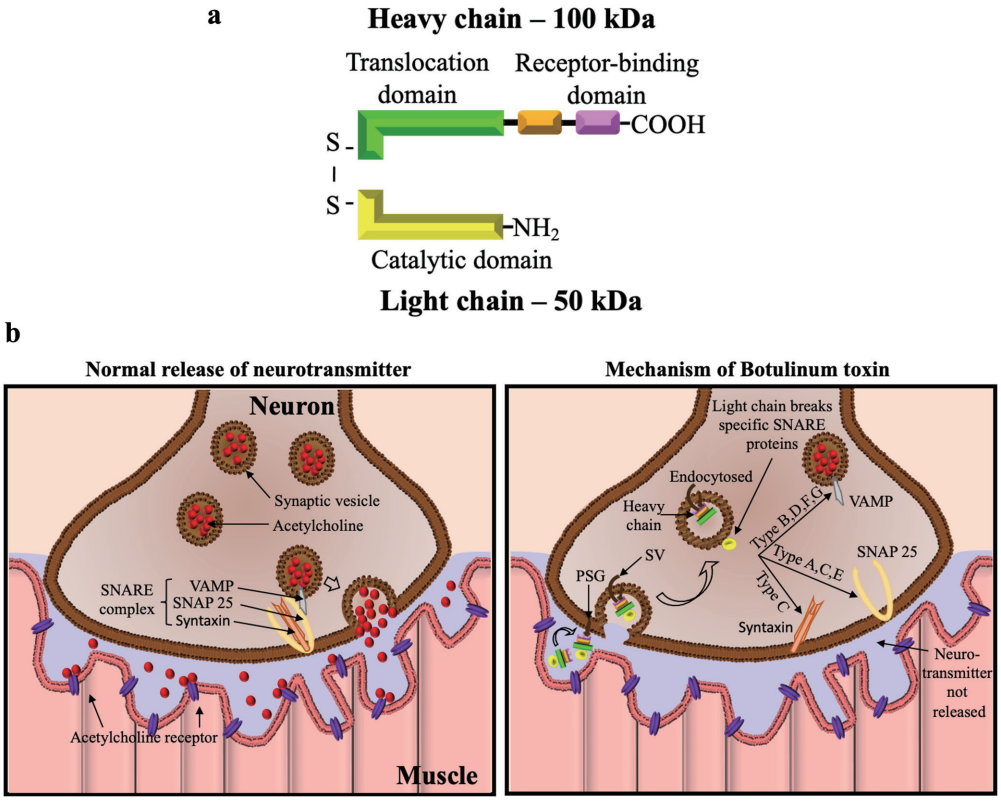

Fig.1. a) Structure of botulinum neurotoxin (BoNT). b) Normal neurotransmitter release requires the fusion vesicle and nerve terminal, which is regulated by the soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) complex. This complex includes vesicle-associated membrane protein (VAMP or synaptobrevin), synaptosomal-associated protein of 25 kDa (SNAP-25), and syntaxin. Acetylcholine is released through the synaptic cleft and attaches to the receptor, resulting in normal muscle contraction. In BoNT, the heavy chain is bound to the polysialoganglioside (PSG) and protein receptors, synaptic vesicle (SV), leading to endocytosis. The acidic environment in the endosome leads to the detachment of the light chain. The light chain translocates into the cytosol and cleaves specific sites on the SNARE proteins, blocking acetylcholine neurotransmitter release.

disorders, and a side effect of eliminating wrinkles at the site of injection in cases of focal dystonia was discovered. This led to the use of BoNT as "Botox" for wrinkles and has created a revolution in the cosmetic field[9].

The United States Food and Drug Administration (FDA) primarily approved BoNT/A to treat strabismus, blepharospasm, and hemifacial spasm in 1989[5,8,10]. Subsequent approval was obtained for its use in the cosmetic field and to treat cervical dystonia, axillary hyperhidrosis, and migraine[11,12]. In recent years, it has been approved for treating lower limb spasticity in children (> 2 years) and adults[13]. Some off-label uses include the treatment of wounds, diabetic neuropathy, temporomandibular disorders, chronic musculoskeletal pain, and urinary and gastrointestinal tract disorders[5]. The use of BoNT/B is limited to cervical dystonia and some cases of hyperhidrosis. The potency of BoNT/B is reported to be considerably lower than that of BoNT/A, necessitating nearly a 40-fold higher dose for the same effect observed with BoNT/A[14,15].

Globally, BoNT is widely used by plastic surgeons and dermatologists. Recently, several off-label uses in the dental fraternity have yielded promising results[1,5]. As it is minimally invasive and provides long-lasting effects with minimal or no side effects, its use in current therapeutic interventions for several orofacial disorders has increased tremendously[10]. This review provides insights for a better understanding of the mechanisms of BoNT and its prevailing clinical use in dental practice.

2. Basic structure and mechanism

Structurally, BoNT consists of three domains: a light chain (L chain, N-terminal catalytic domain); a heavy chain (H chain), which is divided into an internal translocation domain (Hn); and a C-terminal receptor-binding domain (Hc) (**Fig. 1a**). BoNT is synthesized as a single-chain polypeptide of 150 kDa, which is cleaved by endogenous or exogenous proteases into an L chain (50 kDa) and an H chain (100 kDa) that are connected by a disulfide bond[4]. The Hc domain of the H chain binds to the cholinergic nerve terminal, whereas the L chain is a zinc metalloprotease that cleaves proteins that participate in the acetylcholine release mechanism[16]. The amino acid levels of each type of neurotoxin differ by up to 70%. In mice, BoNT/A demonstrated a median lethal dose (LD50) of 1 ng/kg[17].

Physiologically, acetylcholine is released from the cytosol at the NMJ in the synaptic cleft, facilitating the normal signal transfer and muscular contraction. Acetylcholine is released through a

transport protein chain known as "soluble N-ethylmaleimide-sensitive-factor attachment protein receptor" (SNARE), which includes synaptobrevin (also known as vesicle-associated membrane protein [(VAMP]), synaptosomal-associated protein of 25 kDa (SNAP-25), and syntaxin[18] (**Fig. 1b**).

In BoNT, a toxic moiety is present in the L chain, which cleaves SNARE. Each BoNT serotype can cleave different protein targets: BoNT/A, C, and E target SNAP-25; BoNT/B, D, F, and G target VAMP; BoNT/C targets syntaxin[3] (**Fig. 1b**). The Hn domain of the H chain is essential for translocating the L chain across vesicles into the cytosol. The Hc domain of the H chain is required for binding and endocytosis. The L chain must reach the SNARE proteins in the nerve by translocating from the vesicle lumen into the cytosol[19]. When BoNT reaches the target tissue, Hc binds to a ganglioside molecule and a protein receptor found in cholinergic nerve terminals, and BoNT is endocytosed inside synaptic vesicles. Subsequently, the L chain is released into the cytosol with the assistance of the Hn domain, thereby cleaving specific sites on SNARE proteins, leading to the blockade of acetylcholine neurotransmitter release[20] (**Fig. 1b**).

3. Clinical applications of BoNT

The clinical use of BoNT in a wide range of conditions has increased immensely because of its unique sustained pharmacotherapeutic action lasting approximately 3–6 months. Precise knowledge of BoNT and anatomy is necessary for using BoNT in clinical practice. We discussed the most relevant and widely prevailing indications for BoNT in the orofacial region.

3.1. Bruxism

Bruxism is a repetitive oromandibular activity characterized by the clenching and grinding of teeth that can occur both during sleep and in an awake state[21]. Gradually, bruxism leads to temporomandibular joint (TMJ) pain, muscle pain, tooth wear, and damage to dental prostheses[22–24]. The most common treatment option is oral appliances, which can prevent damage to the oral cavity. Occasionally, muscle relaxants and behavioral approaches are also recommended. However, these forms of management only minimize symptoms[25].

The use of BoNT has been reported in several case reports and retrospective studies to treat patients effectively[26–30]. According to a systematic review, BoNT injections reduced the frequency of bruxism when compared with traditional methods[31]. If a patient with bruxism is unresponsive to oral appliance therapy and cognitive behavioral therapy, BoNT has proven beneficial[32]. As a standalone treatment, BoNT is effective in bruxism without the need for oral appliances[33,34]. However, to identify the target masticatory muscles, the measurement of muscle activity is essential[34]. BoNT injections into the masseter and temporalis muscles function by reducing muscle hyperactivity without reducing the frequency, number of bursts, or duration of rhythmic masticatory muscle activity episodes, thus easing masticatory muscle pain[34].

3.2. Myofascial pain

Myofascial pain is characterized by acute or chronic regional muscle pain with single or even several circumscribed painful sites (trigger points) in stretched muscle bands. It is usually associated with stiffness and leads to local or referred pain[35]. Treatment is usually multidirectional and includes behavioral therapy, stretch techniques, low-level laser therapy, ultrasound, transcutaneous electrical nerve stimulation (TENS), cold spraying, and cognitive behavioral therapy[36,37]. Pharmacological management includes the use of muscle relaxants and nonsteroidal anti-inflammatory drugs (NSAIDs)[38].

We recently reported a case of non-odontogenic toothache in which the patient's masseteric muscle tenderness was relieved after a BoNT injection[39]. Several systematic reviews and trials using BoNT to treat myofascial pain in other regions of the body have been reported[40–42]. BoNT injections alleviate pain by suppressing muscular contractions and preventing the release of acetylcholine[42]. However, no previous randomized clinical trials have confirmed the effective treatment of myofascial pain in the orofacial region with BoNT intervention. Further clinical trials are needed to establish the effectiveness of BoNT for treating myofascial pain in the orofacial region.

3.3. TMJ dislocation

Dislocation of the TMJ occurs when the condyle moves forward from its functional position within the glenoid fossa. It causes stretching of muscles and ligaments, leading to pain in the orofacial region. It can be either an acute or a recurrent event, and management varies accordingly[43]. Acute dislocations can be manually repositioned. Recurrent dislocations have a major impact on the quality of life of affected individuals and can be treated with BoNT injections[44]. Surgery is the last-resort treatment for ineffective cases[45].

BoNT injections in the lateral pterygoid muscle were found to be effective for recurrent TMJ dislocation in patients with osteoporosis[46]. A case of chronic recurrent TMJ dislocation in a child was effectively treated with BoNT injection into the inferior lateral pterygoid muscles[47]. BoNT can effectively treat TMJ dislocation by loosening jaw muscles that cause jaw tightness and spasms[47]. However, a recent systematic review reported that limited evidence is available to support the use of BoNT for articular disorders of the TMJ. Further studies with better insights are needed to establish a protocol for treating different TMJ disorders[48].

3.4. Hemifacial spasm

Hemifacial spasm is a chronic condition of the nervous system that causes involuntary twitching of the muscles on one side of the face. An artery contacting or pulsating against the facial nerve is the most common cause of hemifacial spasm. Furthermore, hemifacial spasms could be attributed to facial nerve damage or tumors[49]. Anticonvulsants such as carbamazepine, gabapentin, and clonazepam have been routinely used to effectively treat hemifacial spasms; however, these agents are associated with side effects, such as drowsiness and fatigue[50]. Several clinical trials have reported the successful management of hemifacial spasms with BoNT therapy[51–53].

Currently, BoNT is widely considered the treatment of choice for managing hemifacial spasms[49]. BoNT suppresses the release of neurotransmitters and causes neuro-paralysis. The muscles affected by hemifacial spasm include the orbicularis oculi, zygomaticus major, zygomaticus minor, corrugator supercilli, levator labii superioris alaeque nasi, orbicularis oris, risorius depressor anguli oris, mentalis, and platysma. Guidance with electromyography (EMG) is required to ensure accurate injection placement in facial muscles, and dosages

are typically increased based on the response to therapy[54].

3.5. Orofacial dystonia

Dystonia is defined as an involuntary muscle contraction that leads to rhythmic, repetitive, and atypical movements. When the orofacial region is involved, it is called orofacial dystonia[55,56]. Orofacial dystonia predominantly affects the masticatory muscles. Occasionally, the lower facial muscles and tongue are also affected. It is broadly classified as a jaw-opening, jaw-closing, or jaw-deviation dystonia. Treatment includes the use of anticonvulsants, cognitive behavioral therapy, and physiotherapy[57,58]. BoNT injection has also proven to be promising for managing orofacial dystonia. Superior effects were observed when injections were performed under electromyographic (EMG) guidance[55]. In such cases, BoNT was injected into the masseter and temporalis muscles on both sides. BoNT acts by blocking the release of acetylcholine, resulting in the denervation of muscles[55,59]. BoNT can more effectively treat jaw-closing dystonia than jaw-opening dystonia[56,60]. However, some reports have noted the development of immune resistance to BoNT during oromandibular dystonia therapy[61,62].

3.6. Facial paralysis

Facial paralysis is characterized by an inability to move the muscles of the face. It usually affects one side and rarely affects both sides. It is a congenital condition or may be caused by trauma, brain tumors, or Bell's palsy[63]. The severity of the facial paralysis was determined using several grading systems. The House-Brackmann and Sunnybrook facial nerve grading systems are widely preferred[64,65]. Based on etiology, the management of facial paralysis ranges from pharmacological or physical therapy to invasive surgical methods. In pharmacological management, BoNT has been used since 1987 to treat asymmetries caused by facial paralysis[66].

Knowledge of neural anatomy and the role of facial muscles in expression and function is vital for determining the essential injection areas and injection points[67]. Among conservative approaches, BoNT administration for treating facial paralysis has shown promising results in restoring normal facial features[68]. The use of BoNT has been widely accepted in clinical practice, given its long-lasting and sufficiently adaptable effects to customize the treatment to an individual's requirements. The optimal injection pattern and the dose required to restore facial symmetry in each muscle group remain unknown. However, a previous report has reviewed and summarized an elaboration of dose ranges for each point of injection and muscle group[69].

The assumed mechanism of action of BoNT involves the inhibition of neurotransmitter release, which aids in relaxing stiff muscles. A better prognosis has been reported with the use of combination therapy for the treatment of facial paralysis. Treatment approaches may vary based on the severity and duration of the symptoms and the patient's age[70]. Combining BoNT with mirror therapy or neuromuscular retraining has shown reliable results[69,71,72]. Alternatively, in complex cases, surgical management followed by BoNT administration as a supplement has proven to be a better model than monotherapy[70].

3.7. Chronic migraine

Chronic migraine is characterized by severe headaches for 15 days per month for more than three months. It is an extremely painful and debilitating condition that impacts the quality of life of affected individuals[73]. Episodic migraine often progresses to chronic migraine; however, the exact mechanism remains unknown. Episodic migraine is known to be associated with alterations in nociceptive signals, increased cortical excitability, central sensitization, and structural and functional brain changes[74].

The potential of using BoNT to treat migraine effectively was initially identified after patients who received BoNT for cosmetic purposes reported an improvement in headaches. This led to several clinical trials investigating the use of BoNT in treating chronic migraine, which was approved in 2010 by the FDA[75]. A meta-analysis on the prophylactic treatment of migraine with BoNT has revealed beneficial effects on the quality of life and reduced frequency of headaches[76]. Routine treatment involves lifestyle modifications to avoid triggers and the use of abortive medications (such as topiramate, amitriptyline, methylprednisolone, and valproate) to prevent the occurrence of chronic migraine. In some severe cases where conventional techniques are not beneficial, BoNT was effective as an alternative therapy[76,77]. BoNT is beneficial in migraine management, as it prevents the release of neurotransmitters such as calcitonin gene-related peptide (CGRP) and substance P and aids in preventing the transmission of pain signals to the nerve terminals. However, some studies have reported that additional preventive medications, such as CGRP antagonists, should also be taken along with BoNT injections to obtain optimal benefits[78–80].

3.8. Trigeminal neuralgia

Trigeminal neuralgia is a neuropathic condition that causes intense episodic pain in the orofacial region, including the forehead, eyes, nose, lips, and jaw. It occurs suddenly with intense, stabbing pain and usually affects one side of the face[73]. Classic trigeminal neuralgia is associated with neurovascular compression in the trigeminal root entrance zone. This could result in demyelination and dysregulation of voltage-gated channel expression in the membrane; these alterations account for pain attacks. Secondary trigeminal neuralgia may be associated with underlying tumors, multiple sclerosis, or arterial deformities[81]. Anticonvulsants such as carbamazepine (gold standard) or oxcarbazepine have been the routine treatment of choice[82]. Severe and recurrent cases are managed with surgical intervention and microvascular decompression. However, given the intolerable adverse effects of anticonvulsants and surgical complications, there is a need for new therapeutic options to treat trigeminal neuralgia.

In 2002, BoNT was investigated for its efficacy in treating trigeminal neuralgia and has since been used in research and clinical practice to evaluate its antinociceptive action[83–85]. Several previous studies have documented the use of BoNT to effectively treat trigeminal neuropathic pain[86–88]. The mechanism of action is thought to involve the inhibition of neurotransmitter release, resulting in reduced peripheral and central sensitization[89]. Animal studies have been conducted to determine specific mechanisms of action. Various animal models of neuropathic pain have been used to evaluate the effect of BoNT on pain relief after local injection[89,90]. A recent study by our group has reported the attenuation of neuropathic pain in an animal model and evidence of toxin transmission in neurons of the trigeminal ganglion. Unilateral peripheral injection of BoNT/A in the whisker pad area could attenuate pain bilaterally[91].

Available evidence indicates that it is safe to use BoNT in treating trigeminal neuralgia, as its effects last for several months. This is considered a conservative approach for patients who are unwilling to undergo an invasive surgical approach and do not benefit from conventional pharmacological management. Some reports support the use of BoNT as monotherapy for classical trigeminal neuralgia[88]. Furthermore, BoNT has been beneficial in refractory cases[85].

3.9. Sialorrhea

Drooling or excessive salivation is commonly referred to as sialorrhoea or ptyalis. It usually affects children and adults with neurological impairments such as cerebral palsy and intellectual disability[92]. It can be idiopathic or drug-induced. Sialorrhoea has been attributed to excessive saliva production or failure of mechanisms to cleanse and eliminate saliva from the mouth[93]. Neurologically affected patients lack oral and facial muscle control[94]. The management of sialorrhea involves postural changes, biofeedback therapy, and anticholinergic medications; however, these medications have side effects such as dry mouth, dilated pupils, decreased sweating, and difficulty urinating[92,94]. However, the most effective treatment is surgical intervention involving salivary duct ligation and salivary gland excision because it provides permanent relief. BoNT injection into the parotid or submandibular gland has proven to be effective in temporarily preventing drooling, given that BoNT inhibits cholinergic sympathetic and parasympathetic activities[94]. A previous clinical trial examined the effectiveness of BoNT/A in treating drooling in children with cerebral palsy and showed potential effects after intraglandular injections[95]. In children, BoNT is administered under general anesthesia, with salivary glands located under ultrasound guidance[96].

3.10. Frey syndrome

Frey syndrome is caused by the regrowth of parasympathetic nerve fibers innervating sweat glands and blood vessels in the facial skin. This causes gustatory sweating, flushing, and warmth in the preauricular and temporal areas. Frey syndrome is a complication of frequent parotidectomy, trauma due to incision and drainage of a parotid abscess, or removal of the post-submandibular gland[97]. Medical management includes the topical application of scopolamine or glycopyrrolate (anticholinergics) and topical antiperspirants; however, these agents only provide temporary relief. BoNT administration affords the longest period of symptom relief, with the lowest incidence of complications[98]. A meta-analysis of 22 published case series reported the effectiveness of BoNT in Frey syndrome management[99]. Another report on the long-term follow-up of 100 patients found that the effectiveness of BoNT lasted from 3 to 20 months, with 70% of patients needing two or more injections[100]. BoNT acts by forming a synapse between the parotid and sweat glands, thereby preventing acetylcholine release[99].

3.11. Cosmetics

3.11.1. Gummy smile

A smile with more than 2 mm of gingival exposure is considered a gummy smile, which can affect the esthetic appearance and psychological status of patients. Treatment is usually planned based on the etiology: vertical maxillary excess, short or hyperactive lip muscles, or altered teeth eruption[101]. Routine treatment includes crown-lengthening procedures in the form of gingivectomy and/or osseous surgery and orthognathic surgery in cases of dentoalveolar extrusion[102]. Alternatively, lip repositioning procedures can be undertaken[103].

The application of BoNT was shown to be effective as a non-surgical approach to reduce excessive gingival display[104–106]. The use of BoNT has been reported to produce satisfactory esthetic results, as well as functional restoration of a gummy smile. Furthermore, the combination of BoNT injections with crown-lengthening procedures reportedly produces a better esthetic smile than monotherapy[101].

3.11.2. Asymmetrical smile

An asymmetrical smile is considered to be an embarrassing esthetic problem. An imbalance in the muscle activity between the right and left sides during smiling results in unilateral hyperkinetic activity. Surgical correction by gingival contouring or removal of excessive gingival exposure on the affected side, which is routinely called a smile lift, can be performed. Facial implants are used to correct smiles in cases of skeletal structure deformity. However, these procedures are both expensive and invasive. The use of BoNT to treat asymmetrical smiles has increased in recent years with reported effectiveness. Based on patients' needs, their smiles can be corrected with minimally invasive BoNT injections[107,108].

For treating gummy and asymmetric smiles, the mechanism of action of BoNT involves the prevention of acetylcholine release, thus reducing the pulling action of the lips during smiling[106].

3.11.3. Drooping mouth corners

Aging is well-known to alter the consistency and elasticity of collagen, and accompanied by changes in the cervical commissures of the lips, the remaining facial features appear old or sad. This is predominantly caused by hyperactivity of the depressor anguli oris located bilaterally near the corners of the lips, resulting in a drooping mouth appearance (also called sad, reversed smile, or marionette lines). BoNT has been used to relax the hyperactive muscles at the corners of the mouth. However, because of the anatomical complexity of the depressor anguli oris borders, selecting the ideal injection spot is challenging. The use of an incorrect injection site can lead to complications such as facial asymmetry[109–113].

3.12. Miscellaneous

3.12.1. Chemotherapy-induced neuropathic pain

Chemotherapeutic drugs induce certain common side effects, such as peripheral neuropathy[114]. In our recent study on an animal model of chemotherapy-induced neuropathic pain, unilateral BoNT administration peripherally (whisker pad) effectively attenuated neuropathic pain bilaterally, thereby suggesting a retrograde axonal transport mechanism through the neurons[91].

3.12.2. Facial wrinkles

Facial wrinkles are creases or folds that appear on the skin owing to aging. Wrinkles can be attributed to skin thinning or loss of elasticity over time. Wrinkles usually appear in areas of the face that tend to fold during facial expressions. The most common areas are the forehead rhytids, glabellar lines (frown lines), lateral canthal lines (crow's feet), and wrinkles on the neck. BoNT has been widely used

to temporarily treat facial lines[115,116].

Management involves the injection of 10–20 U of BoNT, 1 cm above the orbital rim, to avoid injection into the glabella, given the possibility of brow ptosis. Low doses are preferred to avoid a frozen appearance[117]. Frown lines were treated with 20–40 U BoNT injected over five paired injection sites[118]. Crow's feet are managed by injecting 8–16 U of BoNT into the lateral orbicularis oculi, 10–15 mm away from the orbital rim, to prevent diffusion into the extraocular muscles[116]. Wrinkles due to platysma were managed by injecting 2–4 U of BoNT at six points along the jawline[119].

3.12.3. Perioral rhytides (smokers lines)

Perioral rhytides are lines that appear in the upper and lower lip regions of chronic smokers. These lines have been attributed to repeated contraction of the orbicularis oris muscles and the narrowing of the blood vessels induced by the nicotine content in cigarettes, causing smokers to experience premature aging when compared with non-smokers[120]. Cosmetic management of these lines involves the use of BoNTs, dermal fillers, or a combination of both. BoNT injections can treat these lines and provide more fullness to the lips[9].

Injection of 1–2 U BoNT along the vermilion border has been administered at 2–4 sites. Patients may experience adverse effects, such as difficulties swimming, enunciating, spitting, and using a straw. In addition, this treatment may cause asymmetry[121].

3.12.4. Masseteric hypertrophy (bulky jaws)

Unilateral or bilateral enlargement of the masseter muscle can result in bulky jaws, and causes include chronic clenching, habitual asymmetric chewing, TMJ dysfunction, and congenital factors[122]. It is an asymptomatic condition, but patients experience dissatisfaction owing to its unaesthetic appearance. Routine management involves surgical reduction of the masseter muscles, which may lead to several complications, such as restriction of mouth opening and nerve paralysis post-surgery[123,124]. Ideal management involves BoNT injections, which weaken the muscles, thereby reducing their bulky appearance[125]. Occasionally, BoNT treatment is combined with postsurgical treatment to achieve better jawline contouring. Ideally, the injection sites should lie below the line joining the lobule and labial commissure. Injections of 5–15 U BoNT were placed at three sites. This positioning prevents the cheeks from appearing sunken[126,127].

Table 1 elaborates on the speculated mode of action, recommended dosage, site of injection, alleviation of symptoms, and side effects of each clinical aspect [10,21–23,26–29,34,40–42,44,46,49,50,54–56,67,69,70,74,75,84,86,89,94,95,97,99–101,104–109,111,128–167].

4. Preparation and application techniques

BoNT is commercially available under various trade names. BoNT injection is routinely administered using a fine-gauge needle (27–30G). As an adjunct, some physicians prefer to use EMG guidance to administer BoNT injections, thereby ensuring accurate muscle targeting, causing hyperactivity or hyperfunction[136,168,169]. As a precautionary measure, the patient was advised to avoid any strenuous activity or massage for up to two weeks after the injection. Therefore, follow-up and monitoring are essential. As repeated injections are required, the lowest effective dose should be administered initially and at well-spaced intervals to reduce the risk of antibody development.

5. Toxin immunogenicity

BoNT is considered a foreign substance by the host and has the potential to induce an immune response. This may lead to successive treatment failures in cases of repeated administration[170]. Botulinum toxin consists of neurotoxin and non-toxic NAPs. Neurotoxin is the only therapeutically effective component; the proteins are antigenic and can provoke an antibody response[171]. In Botox® and Dysport®, 150 kDa neurotoxins associate with non-toxic NAPs and form large complexes. Xeomin® is highly purified; the neurotoxins are free and are suggested to have reduced immunogenicity when compared with Botox® and Dysport®[172]. Newer preparations utilize the protein load in the composition to reduce the risk of immune resistance. To effectively use BoNT for therapeutic purposes, physicians should perform repeated injections over prolonged intervals.

6. Contraindications

Patients with the following conditions should not be treated with BoNT or treated with extreme caution[116,173]:

- Allergic or hypersensitivity reaction to any of the constituents of BoNT
- Any infection at the site of injection
- Pregnancy and lactation (the FDA has categorized BoNT as a category C drug, which indicates that the safety profile of BoNT has not yet been fully evaluated for nursing mothers and pregnant women[174])
- Psychological illness
- The use of medications such as calcium channel blockers, aminoglycosides, and other drugs is known to interfere with neuromuscular impulse transmission (patients should be carefully observed, as these medications can potentiate the effect of BoNT. Aminoglycosides may prevent acetylcholine release into the NMJ and cause a botulism-like state. Cyclosporins may induce muscle weakness secondary to neuromuscular blockades. Ideally, these drugs should be discontinued or stopped for a short duration under the guidance of a physician before BoNT administration[174,175])
- Neuromuscular disorders (patients with myasthenia gravis, multiple sclerosis, or Lambert-Eaton syndrome are at an increased risk of developing adverse reactions such as ptosis, diplopia, dysphagia, dysarthria, and dysphonia, given that BoNT may worsen the existing state of compromised neuromuscular transmission[174,176])

7. Serious side effects and management

- BoNT may cause allergic reactions, which can be prevented by identifying previous allergic reactions to other brands or constituents of BoNT. If the allergy or erythema persists beyond 24 h, an antihistamine can be administered. In cases of an anaphylactic reaction, emergent medical conditions should be treated under medical supervision. Adrenaline injections and continuous close monitoring of the patients are recommended[174,177].
- Large doses for cosmetic correction and injections in the platysma region may cause dysphagia. The muscles in the neck

Table 1. List of clinical applications of botulinum toxin (BoNT) in head and facial region

Clinical application	Speculated mode of action	Recomm ended dosage	Effective site of injection	Alleviation of symptoms	Side effects
Bruxism	Injection of BoNT into masseteric and temporalis muscle reduces the intensity of muscle contraction thereby reducing the masticatory muscle pain and dysfunction caused by muscle hyperactivity[34].	Dosage range of 15-60 U, ideally 25 U is effective[26–29,34].	The nerve innervation site of the affected muscle, i.e., the bulkiest area of the muscle (masseter or temporalis) is considered the richest nerve branching site[21–23,34].	Reduces bruxism induced pain. Reduces the frequency of jaw motor activity in bruxers. Improved symptoms of morning jaw stiffness[31,34].	Decreased sensation of masticatory force. Discomfort and muscle weakness[33,34].
Myofascial pain	Injection of BoNT into the trigger point blocks the communication between the muscles and nerves. Thereby providing pain relief by inhibiting muscle contractions and preventing the release of acetylcholine[42,128].	Dosage range of 5-50 U/ site was reported to be effective for other regions[40,41].	Center of the trigger point. In the case of masseteric muscle, the upper and lower portions separately, temporalis can be injected at the central portion[40–42].	Effective pain relief and less muscle fatigue were reported, however, lasts only to a maximum of 30 days from the time of injection[128].	Slight pain in the injection site, no other reported side effects[40–42].
TMJ dislocation	Injection of BoNT relieves jaw tension and spasm by disengaging the responsible jaw muscles[129].	25-50 U/muscle in one or two injections respectively is predominantly reported to be effective[44,46].	Extra orally into the lateral pterygoid muscles bilaterally through the sigmoid notch[46]. In a few cases, the injection can be given at two sites. The first is given into the space formed between the zygomatic arch and the sigmoid arch of the mandible, and the second is approximately 0.5-1cm posterior to the first injection site immediately in front of the mandibular condyle[129].	Symptoms of pain are relieved, and patients have reported no further dislocations six months after the procedure[46].	No reported immediate or delayed side effects.
Hemifacial spasm	Administration of BoNT acts by inhibiting the release of neurotransmitters thereby leading to neuro paralysis[54].	The recommended dose ranges from 10-30 U, should be started at a low dose and increased if required based on the therapeutic response[49,130].	Multiple injection sites i.e., the muscles of facial expression. Orbicularis oculi and platysma can be easily injected subcutaneously by visual inspection, other muscles require EMG guidance for accurate needle placement[131].	BoNT serves as a temporary remedy as several high-quality clinical trials have reported that 76 – 100% of patients have recovered 75% with BoNT therapy lasting for 3 – 4 months[53,132–134].	Very few cases report mild facial paresis, ptosis and diplopia[50,135].
Orofacial dystonia	Injection of BoNT blocks the release of acetylcholine which leads to chemical denervation of skeletal muscles in a short term[55].	The dosage varies depending on the severity of dystonia and the muscle affected. The average dose injected per site is 2.5-5 U, total average dose of injection used is 25 U[136].	The site depends on the type of muscle affected. The number of injection sites varies and can be increased based on the patient's response. EMG guidance ensures the precise location of drug delivery and improves the therapeutic effectiveness[55].	Reported to create a major reduction in dystonic hyperactivity[56,136]. In some cases, satisfactory results are not observed, in such cases stimulation of globus pallidus internus has shown alleviation of symptoms[137].	In lingual dystonia, muscle weakness at the injection site, speech, and swallowing difficulties[138]. Based on the dose in some cases, loss of smile and jaw tremors have been reported[55].
Facial paralysis	The injection of BoNT works by blocking the release of neurotransmitters which relaxes the affected muscles that are extremely stiff, thereby preventing involuntary facial movements or synkinesis[70].	The effective dose varies based on the severity of the synkinesis or hyperkinesis[139]. Ideally, it is recommended to inject lower than the normal (1-3 U/ point) during the initial sessions as the follow-up after two weeks gives a clearer idea of the patient's requirement[69]. Further after multiple sessions, a customized dose chart can be created[67].	Based on the severity and affected muscles, the depth and angle of the injection needle are important to consider as it helps in preventing paralysis of unwanted muscles, ptosis, diplopia, etc[67,69,139].	Reduces spasm, synkinesis and hyperactivity of muscles of facial expression[10,140].	Caution is important while treating patients with chronic facial palsy as BoNT injection could lead to further weakness of the muscles rather than reducing the synkinetic movements[141].

Table 1. *Continued*

Clinical application	Speculated mode of action	Recomm ended dosage	Effective site of injection	Alleviation of symptoms	Side effects
Chronic migraine	BoNT is effective in treating migraine as it blocks the neurotransmitters released like CGRP, substance P, etc, thereby preventing the pain signals before they reach the nerve endings[142–144].	Based on the trials of Phase III Research Evaluation Migraine Prophylaxis Therapy (PREEMPT) an injection paradigm has been established which necessitates at least 31 injections of 5 units per site[145,146].	Specific points in frontal, temporal, glabellar, temporal, upper cervical and trapezius. Additionally, more injection points can be administered as a "follow the pain" option (occipital, temporal and trapezius regions) [74,147].	Reduced frequency of migraine episodes and improvement in quality of life[145–147].	Muscle weakness, diplopia, blepharoptosis and skin tightness are some of the mild side effects reported[75]. Additionally, poor injection technique would increase the risk of brow and eyelid ptosis, neck pain and shoulder pain[74].
Trigeminal neuralgia	BoNT has an antinociceptive effect, it inhibits the release of neurotransmitters and is hypothesized to reduce peripheral and central sensitization in the trigeminal system[89,148].	Injection dose of 2.5-5 U per site with 10-15 mm between injection sites, a total of 75-100 U dosage[86,149].	Intradermal and/or submucosal injection of BoNT is administered along with the territory of pain (course of trigeminal nerve branches) [87].	The severity of pain and the frequency of attacks per day were significantly reported to be reduced after 2 weeks from the initial injection[84].	Injection site swelling and mild eyebrow ptosis[85,86]. Few cases have reported facial paralysis, slight facial asymmetry, facial edema, etc[150–153].
Sialorrhea	Injection of BoNT into the salivary glands inhibits the cholinergic parasympathetic and sympathetic activity thereby reducing the salivary output[154–156].	Injection of 10-40 U into each salivary gland[94,95]	Occasionally BoNT is injected in both the submandibular and parotid glands, but a majority of the researchers have chosen to inject only the submandibular gland based on the assumption that it produces most of the resting saliva[95,157]. Additionally restricting injection to the submandibular glands alone would aid in the continued functioning of the parotids allowing for mastication and digestion effectively[157,158].	A series of trials revealed that it reduced salivary flow by approximately 40% in a majority of the patients[157–160].	Excessive oral dryness and eating difficulty due to inadequate lubrication of food bolus if both submandibular and parotid glands are injected. Pain at the site of injection[160,161].
Frey syndrome	Injection of BoNT creates a synapse between the parasympathetic parotid fibers and sweat glands thereby leading to blockage of acetylcholine release[99,162,163].	Intradermal injection of 5-10 U/ injection site (usually 3 or 4 sites). The distance between the point of injections should vary from 10-20 mm. The maximum dose is not more than 380 U per patient[99,100].	The affected area is marked with the Minor's starch iodine test. The area is further subdivided to mark the inter-injection distance and BoNT is injected intradermally[163].	BoNT should be considered the treatment of choice as it is very effective in the treatment of Frey syndrome with effects lasting up to a maximum of 20 months[99].	Pain at the site of injection initially[100]. Very few patients have reported having a dry mouth or transient muscle weakness which resolved within 12 weeks[97].
Cosmetic Gummy smile	Intramuscular injection of BoNT causes partial denervation of the muscle by preventing the release of acetylcholine which results in reduced muscle activity. It prevents the pulling up action of the lips during smiling[101,106].	The injection starting dose of 1.25 U BoNT per muscle site. In some cases, the ideal effective dosage has been reported as 2.5 U per site[104,164]	Injection sites include levator labii superioris, levator labii superioris alaeque nasi, levator anguli oris, zygomaticus major, zygomaticus minor and depressor septi nasi. Injections are routinely given bilaterally, and the sites are located by asking the patient to smile[104,165].	The excessive gingival display was reduced after two weeks of BoNT therapeutic injection; however, the effect is temporary with an average improvement lasting about 3-6 months[104,105].	Precaution is required in frequent injection as it is only a temporary correction, it can lead to muscle weakening or an unesthetic smile appearance due to excessive soft tissue covering the smile line[104]. Some cases have even reported muscular atrophy and a permanent decrease in the ability of muscular contraction even after the toxic effect has disappeared[164].
Asymmetrical smile	Same as above	Unilateral injection of 2-3 U of BoNT has shown to be effective with positive results[107,108].	Unilateral intramuscular injection at the Yonsei point (confluence of three muscles – the levator labii superioris, levator labii superioris alaeque nasi and zygomaticus minor) to the most elevated side if there is upper asymmetry. For lower asymmetry, BoNT is unilaterally injected into the depressor labii inferioris muscles and depressor anguli oris[107].	The asymmetry was corrected and the balance in the muscle activity is achieved on both sides during smiling. Effective within 1 week and the symmetry lasted for 6 months after the initial injection[107].	If a minimal dose is not used for injection excessive weakening of the muscles may occur and may also cause overcorrection[166].
Drooping mouth corners	Intramuscular injection of BoNT relaxes the depressor muscles which lifts the drooping lip corners[109].	A dose of 2-5 U of BoNT is injected routinely[111].	Bilateral superficial injection on the trajectory of the nasolabial fold to the jawline[108].	BoNT injections have been reported to relax the depressor muscles providing an improved appearance of the aged face look[167].	Due to the anatomical complexity of the borders of depressor anguli oris muscle, an improper injection may result in slurred speech, drooling and lack of facial expression. Besides these, if the injection is placed more medially it may cause lower lip protrusion[109,111].

region are more prone to the diffusion of botulinum toxin, which occasionally may also cause dysphonia. Mild dysphagia can be managed with a soft diet. However, severe dysphagia may require immediate medical attention to aid in nasal feeding and maintaining water-electrolyte balance through intravenous nutrition[174].

- Another serious adverse effect of BoNT is muscle weakness, which may be associated with dysphonia, dysphagia, headache, dizziness, and even respiratory arrest (botulism). Botulism is dose-dependent and occurs because of toxin diffusion from the injection site into the adjacent muscles, even when separated by fasciae. An interesting fact to note is that muscle weakness can occur at any stage of treatment. Clinicians have even reported cases one year after the initial injection. Severe botulism with respiratory failure requires ventilator support and tracheal intubation. Close monitoring of vital signs is essential, and the administration of botulinum antitoxin serum has proven efficacy[174,178].

8. Safety precautions[116,173,174]

- The dentist should be aware of the previous history of BoNT injection.
- The patient's medical history, allergy history, and underlying clotting disorders should be considered before BoNT therapy. Patients taking blood-thinning medications (aspirin or warfarin) may need to temporarily stop the drugs under a physician's advice to avoid the risk of bleeding and bruising.
- Patients should be advised not to massage or rub the injection site for 24 h as it may interfere with spreading the toxin to adjacent sites.
- Patients should be instructed to avoid further skin treatment or application of any product at the injection site.
- Patients should be advised to avoid alcohol intake before and after BoNT injection for at least 24 h.

9. Implications for future clinical practice and research

Limited evidence supports the use of BoNT in routine clinical practice to treat orofacial pain. Currently, there is a lack of data from randomized controlled trials on several applications of BoNT. Furthermore, several large-scale studies involving large populations are required to confirm the benefits of BoNT in dental therapy. Researchers should employ study designs such as randomized controlled trials, observational studies, placebo-controlled trials, and effectiveness studies (also known as pragmatic studies), as well as guidelines for reporting results[179,180]. Future studies should document the outcomes, quality of life, long-term effects, type and dosage of BoNT used, side effects, and follow-up.

10. Summary

BoNT is a promising therapeutic toxin for a multitude of orofacial applications. In the present review, we provide a detailed, updated overview of currently available clinical applications. BoNT is a safe treatment that can be used effectively, provided that the clinician has adequate knowledge regarding the underlying mechanism, injection techniques, and local and systemic side effects and that administration is performed cautiously and purposefully.

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Conflict of interest

The authors declare no conflict of interest.

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