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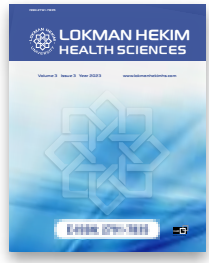

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REVIEW

Botulinum Toxin: A Review of Cosmetic Applications and Hyperhidrosis Treatment

Botilinum Toksin: Kozmetik Uygulamalarının ve Aşırı Terleme Tedavisindeki Yerinin Derlemesi

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Abstract

Injections of botulinum toxin for the treatment of face wrinkles are the most popular cosmetic operation both internationally as well as in Turkey. The U.S. Food and Drug Administration has approved the treatment of frown lines, crow's feet, and horizontal forehead lines as aesthetic purposes. This procedure produces predictable results, with a few side effects, and is linked to high patient satisfaction. A potent neurotoxin, botulinum toxin prevents acetylcholine from being released at the neuromuscular junction. Compared to static wrinkles, which are evident at rest, dynamic wrinkles, are seen during muscular contraction and produce more striking results. In this evaluation, only uses for aesthetics and hyperhidrosis will be investigated thorougly.

Keywords: Aesthetic; Botulinum toxin; Cosmetic; Drug analysis; Head and neck; Hyperhidrosis; Women's health

Botulinum neurotoxin (BoNT), a protein with a high molecular weight, has a molecular weight of 150,000 daltons and is naturally generated by the anaerobic, gram-positive, spore-producing bacillus Clostridium botulinum.[1] So far, seven serotypes of BoNT (A-G) have been identified, and only types A and B are available for therapeutic use.[2]

As a microbiological student of Robert Koch, Professor Emile Pierre van Ermengem was the first to describe the C. botulinum bacillus.[3,4] Dr. Alan Scott, an ophthalmologist, carried out the toxin's initial clinical studies between the late 1960s and the beginning of the 1970s. BoNT-A received its initial Food and Drug Administration (FDA) approval for the treatment of strabismus, and in the beginning, it went under the name Oculinum.[5] BoNTA's non-surgical correction of adult strabismus, blepharospasm, hemifacial spasms, and Meige syndrome was first authorized in the United States in 1989 by manufacturer Allergan Inc. (Irvine, CA). Since then, its clinical application has grown to encompass the treatment of cervical dystonia and spasmodic torticollis.[6–8]

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Table 1. Botulinum toxin types approved by the FDA (ones that are found in Türkiye are marked in red)[10]

	DA	OA	AA	IA
Molecular weight (kDA)	150	900	Approximately 400	150
Stabilization	Lyophilization	Vacuum drying	Lyophilization	Lyophilization
Solubilization	Normal saline	Normal saline	Normal saline	Normal saline
Shelf life once reconstituted (hours)	72	36	24	36
Can be stored at room temperature unreconstituted	Yes	No	No	Yes
Glabellar line dose (U)	40	20	50	20
Mass of core neurotoxin in glabellar line dose (ng)	0.18	0.18	0.27	0.08
Glabellar line response rate (%)	74	NA	52–60	48–60
Median duration of effect	24 weeks/6 months	3–4 months	Up to 4 months	Up to 3 months

DA: DaxibotilinumtoxinA; OA: OnabotilinumtoxinA; AA: AbobotilinumtoxinA; IA: IncobotilinumtoxinA.

In 2002, the FDA authorized BoNTA for the treatment of glabellar lines. In 2017 and 2013, respectively, the FDA authorized BoNT-A when treating forehead and lateral canthal lines.

Mechanism of Action

BoNT selectively and reversibly inhibits the presynaptic neurotransmitter acetylcholine.[9] After being taken to the presynaptic nerve terminal, the active toxin's heavy chain binds to synaptic vesicle glycoprotein 2 and speeding up the process of taking the toxin-glycoprotein complex into the cell and releasing the toxin light chain into the synapse space. The toxin's light chains cut the vesicle-associated membrane protein/synaptobrevin (BoNT-B, D, F, G) or synaptosomal-associated protein 25 (BoNT-A, C, E). This stops the release of acetylcholine from peripheral motor neuron axons, causing muscle weakness.[10]

Today, there are 6 different Botulinum toxins approved for use by the FDA. These; OnabotilinumtoxinA (California, USA), AbobotilinumtoxinA (Arizona, USA), Incobotilinumtoxin A (Frankfurt, Germany), PrabotilinumtoxinA-xvfs (Seoul, South Korea), DaxibotilinumtoxinA-lanm (Tennessee, USA) and Rimabotilinum (California, USA) (Table 1).[9–11]

Upper Face Treatment

Anatomy

For facial expression to function as a communication tool, there must be a complex interaction between the facial muscles and the skin that covers them. When the face muscles are contracted, facial rhytids are produced as a result of these linkages as well as the directional orientation of the muscle fibers. Terminal branches of the facial nerve innervate the muscles that control facial expression. In the periorbital region on both sides, the pairs of orbicularis oculi (OO) are organized in a manner that is circular. The supraorbital, supratrochlear, infraorbital, and angular arteries supply them. Along with the procerus and depressor supercilii muscles, the OO plays a role in eye closure and is a major brow depressor. The frontalis muscle raises the brow in opposition to the OO's brow depressor action. The contraction of the OO muscle results in the formation of lateral canthal lines, in a pattern that is reminiscent of the spokes on a bicycle wheel. It is commonly referred to as "crow's feet".[12] The OO can be targeted to perform a lateral brow lift because it is the main depressor of the lateral brow.[13] The corrugator supercilii (CS) works to move the eyebrows inferior and nearer the midline.[14] The CS muscles are interesting because they are deep to the frontalis in the middle and shallow to the frontalis on the sides. The "11's",[15] or vertical forehead wrinkles between the brows, are a result of this muscle contracting.

Studies comparing the dosages of OnabotilinumtoxinA (Botox) and AbobotilinumtoxinA (Dysport) have shown that to have the same therapeutic effect as 1 IU of OnabotilinumtoxinA, the typical dosage of AbobotilinumtoxinA required is between 2 and 4 IU.[16] The most appropriate dose equivalence, according to many experienced clinicians, is between 2.5 IU of AbobotilinumtoxinA and 1 IU of OnabotilinumtoxinA. Additionally, 20 IU of OnabotilinumtoxinA and 50 IU of AbobotilinumtoxinA are FDA-approved dosages for the glabella. In a double-blind, randomized study comparing the conversion ratio of 1: 2.5 (OnabotilinumtoxinA: AbobotilinumtoxinA) for the treatment of mild and moderate facial wrinkles, both medications demonstrated comparable changes from baseline at 8 and 12 weeks. The 16-week follow-up revealed disparities, with OnabotilinumtoxinA having a longer duration of effect, indicating that a higher dose of Abobotilinum-

Table 2. BoNTA in Glabellar area[24]

Location/sites	Muscle	Dose BoNTA-ABO	Dose-BoNTA-ONA
Glabella	Corrugator supercilii-medial-lateral-procerus	50–100 U total	20–50 U total

toxinA may be necessary to achieve duration parity.[16] According to an investigator review of a dosage study comparing AbobotilinumtoxinA to OnabotilinumtoxinA at a ratio of 1–4 for the aesthetic treatment of hyperfunctional facial lines, such as transverse forehead rhytides, AbobotilinumtoxinA was statistically better at erasing horizontal lines.[17] The investigators concluded that a higher dose ratio of OnabotilinumtoxinA: AbobotilinumtoxinA can be used in the upper face safely because the adverse event profile did not demonstrate any variations between the various formulations.[17]

The two commonly used BoNTA formulations may demonstrate differing diffusion tendencies from the injection site, according to several lines of research. Different "areas of influence" or surface areas are affected by the toxin depending on the toxin's "spread" or diffusion rates from the injection site. Certain regions of the upper face with small, thin, and tightly spaced muscles have significant clinical implications for the probability of diffusion. Although some earlier studies suggested that AbobotilinumtoxinA may have a higher potential for diffusion than OnabotilinumtoxinA,[18] other studies have produced conflicting results regarding whether the higher potency improves clinical outcomes and patient satisfaction and whether BoNTA can be used to plan patient migration.[19] To maximize its potential, more investigation is required.

Glabella

The most popular cosmetic application of BoNTA is injection into the glabella. The majority of patients can benefit from the typical five-injection site strategy, which involves two injections in each corrugator and one in the procerus. In most cases, the muscles that are immediately recognized at maximum frown are the procerus and medial corrugators. Where it enters the dermis and medial to the midpupillary line, the lateral corrugator is injected a little more superficially. In women and individuals with modest to moderate levels of muscle mass and a moderate frown, the recommended total dose of BoNTA-ABO is 50 IU, distributed equally over the course of five injections. However, rarely surpass a total dose of 80 IU in any patient.[20] A greater dose of toxin can be utilized in men, and patients with bulky corrugators may add two more injections at the mid-pupillary line. Subjects above the age of 50 responded less strongly than those under the age of 50.[21] When treating glabellar rhytides, increasing the dosage of BoNTA-ABO over a certain point has no appreciable impact on effectiveness.[22]

In order to feel for the tense muscle, the physician can instruct the patient to pull their medial brow in toward their nose and relocate their eyebrows to the middle. In order to avoid the frontalis muscle, which is located more superficially, the provider should inject this area deeply (supraperiosteally). The insertion of the muscle may be observed when the patient contracts the muscle laterally since this is when the skin on the patient's forehead above puckers. To avoid the frontalis in this area, a shallow injection should be used.[23] The corrugator should be injected 1 cm above the superior brow in order to prevent toxin from diffusing into the levator palpebrae superioris (LPS) and causing ptosis, and the patient should remain upright for 2–3 h following the injection.[14] To prevent dissemination, further precautions need to be taken to guarantee that the vast majority of the corrugator injections are performed gently and superficially. The dosages of BoNTA in the glabellar area are shown in Table 2.[24]

Blepharoptosis is a significant side effect of toxin injections in this location. Patients should be instructed on suitable post-injection behaviors, such as refraining from massaging the treated areas or lying flat for 3–4 h after treatment and refraining from specific physical activities.[25,26] The use of pre-treatment photos is crucial for establishing an impartial baseline. This is crucial for individuals who have asymmetric eyelids or brows because, according to estimates, 90% of people have asymmetrical brows.[27]

Treatment of Forehead Wrinkles

The forehead region is crucial in facial rejuvenation using botulinum toxin because wrinkles on the forehead are one of the earliest signs of aging. Although only the glabellar lines and lateral canal wrinkles (Crow's foot) are FDA-approved BoNTA injection sites, doctors frequently inject the drug into the forehead region to smooth out horizontal forehead lines. The frontalis is injected intramuscularly or superficially, right beneath the subcutaneous tissues. In order to prevent ptosis, injections are often administered at least 1.5 cm above the superior orbital rim.[28] Less likely to result in brow or lid ptosis are injections into the middle

Table 3. Forehead treatment with BoNTA[29]

Target indication	Muscles involved	Recommended No. injection points	Total starting dose/botox
Horizontal forehead lines	Frontalis, possible interactions with procures, corrugators, and orbicularis oculi	4–9, spaced at least 1 cm apart and dictated by overall forehead shape	Women: 6–15 U Men: 6–15 U

and upper parts of the frontalis. The current recommended total starting dosage for injecting the forehead in women is around 6–15.5 BoNTA for the BoNTA-ONA formulation, in 3–5 aliquots. The general opinion is to start with 6–15.5 for males as well; however, due to the larger amount of muscle in men, higher dosages are commonly used. When compared to women with comparable wrinkle levels, men will often need an additional 25–50% of toxin for treatment of the forehead (particularly for those who want the muscle to be well immovable). The BoNTA treatment doses for the forehead are shown in Table 3.[29]

BoNTA injections into the forehead typically involve four to nine injection sites. A wide forehead is defined by a vertical distance of more than 70 millimeters between the glabella and the frontal midline hairline, which may be helped by two rows of injection sites. A narrow forehead is defined by a vertical length of less than 60 mm and is frequently treated with a single row of injection sites.[30] BoNTA's effects are not restricted to the injection site. The toxin's action spreads over a region of around 3 cm in diameter when it diffuses into the nearby tissue. Due to toxin dispersion, there is a higher risk of brow asymmetry and ptosis in patients with extremely narrow foreheads. Injection sites should often follow the natural curve of a woman's brow so that she can keep her natural arch. Rhytides are more frequently found in the superior part of the frontalis, close to the hairline, in men. After mid-forehead injection, more superior frontalis fibers may be recruited in men with receding hairlines, which could result in the development of new rhytides superiorly at the frontalis' attachments to the galea. It's critical to recognize the possibility of the mechanism of compensation and administer at least two rows of injections to balding patients. When a patient exhibits excessive eyelid skin, also known as dermatochalasis, it is recommended to avoid treating the horizontal forehead line that is the most inferiorly positioned.[30] When using BoNTA rejuvenation in conjunction with fillers, it is recommended to stage the procedures, treating first with BoNTA and subsequently with filler.[31] It has been demonstrated that doing so boosts the longevity of the filler correction and allows for the evaluation of any remaining static lines following the start of BoNTA activity.[31] The most crucial factor in all combination treatments is documentation of the injection sites and units used.

The most significant potential risk associated with BoNTA injections into the forehead is a condition known as brow ptosis. Injecting too superficially in the medial corrugator, injecting too inferiorly in the frontalis, not to inject the opposing OO muscle and glabellar muscles, and administering too much volume in comparison to the opposing muscles are some of the ways that frontalis injection can result in ptosis of the eyebrow position. Blepharoptosis can also happen when a hidden pre-existing LPS deficiency manifests itself. This issue is very transient and will totally resolve in 3–4 months. However, some individuals with lateral brow ptosis may benefit by injection of the superior part of the lateral OO area. It will produce an effective brow lift by relieving the natural downward pressure of the OO. It is advised to avoid treating patients with significant frontalis compensation for brow ptosis at baseline, which is common in older patients, and injections should be given at least 1.5 centimeters above the brows, and preferably at much lower dosages. Like with most cosmetic treatments, you may always add extra product to fix any damage rather than doing too much at once. In elderly people, who rely more on the frontalis to raise the brow, a lower starting dosage of any BoNTA formulation is recommended. The hazards of brow ptosis and the likelihood that surgery will be more effective in achieving the desired aesthetic outcome should be clearly explained to this subset of individuals.[25]

When the frontal portion of the forehead is paralyzed yet the fibers of the lateral frontalis remain untouched, the eyebrow can take on a quizzical or cockeyed expression (Mephisto or "Mr. Spock" brow). It is possible to resolve this situation by injecting between 1 and 3 IU of the Botox formulation into the untreated lateral fibers that are responsible for movement to the upward. Consistent method may nonetheless lead to some asymmetry because patients vary naturally. In the event that one side responds more rapidly than the other, it is important to evaluate any claims of asymmetry at least 10 days following treatment. This will allow for the full commencement of the influence that the BoNTA will have.[27]

Treatment of Periocular Wrinkles and Crow's Feet

The greatest candidates for periocular botulinum toxin injections are individuals who have deep lateral canthal rhytides and/or who make a "pit" in the pretarsal orbicularis muscle under the eyelid edge when smiling. Eyelid skin is thin, and there isn't much subcutaneous tissue underneath. Brow ptosis occurs slowly, and many people who are affected are unaware of the alteration. The size and the form of OO muscle have no influence on the toxin's dose or pattern of distribution. The idea of a "standard" dose and distribution pattern of botulinum toxin does not apply in the periorbital region, despite the creation of basic guidelines being possible. The term "crow's feet" refers to lines that emerge from the lateral canthal area in a fan-shaped dispersion. One of the earliest indications of aging may be these lines. The lateral periorbital area is prone to wrinkles since the skin there is naturally thin and abundant. Apart from the skin laxity, contraction of the zygomaticus major may also contribute to the development of these lines. The OO muscle is the sole cause of these lines. The static look will be improved over time by BoNTA injections, but to a lesser degree. The periorbital skin is pushed upward when the zygomaticus muscles contract, which must be differentiated from the action of the OO muscle. The latter condition is challenging to cure without causing face drooping or an unnatural appearance since overusing the zygomaticus muscle may lessen the elevation and fullness of the cheeks that naturally accompany smiling. Only lines caused by contraction of the OO muscle should be treated with BoNTA.[32] The safest strategy is to use the smallest effective dose of the toxin to achieve the desired therapeutic effect. Start slowly and gradually increase over the course of a few weeks as needed. BoNTA can also be utilized to weaken the pretarsal OO muscle as a subtle yet efficient periocular therapy. In people with "hypertrophic" OO muscle, this can lessen the noticeable "roll" with smiling and enlarge the palpebral fissure. However, additional eyelid skin or excessive activation of the zygomatic muscles might be to blame for the "picking up" of the lower eyelid in certain persons when they smile. The lower eyelid botulinum toxin injection will not considerably help these patients.

The therapeutic objective, the mass of the OO muscle, and the placement of the globe in relation to the orbit should all be taken into consideration when determining the amount of BoNTA to be injected in this region. It is possible for the OO muscle to have a dramatically different size and distribution in each individual patient, and even within a single individual, the size and distribution of the muscle can vary significantly from one side of the face to the other.[33] While upper fan was relatively unusual, full fan, lower fan, and middle fan patterns were seen in almost one-third of patients at rest and animation, respectively. Larger doses of toxin than may be deemed "standard" are needed for those with muscle that is dispersed widely or who have relatively hypertrophic muscle. Similarly, patients with less powerful muscles should get toxin doses that are substantially lower. Because individuals with prominent globes owing to shallow orbits, eye disease related to thyroid disfunctions, or myopia have a higher risk of ectropion, the dose should be reduced when injecting the lower eyelid and inferior lateral canthal area.[33]

When treating this area, it is advised to consider the amount of IU per injection site rather than the total dose. In the lateral canthal region, 2.5–5 IU of BoNTA–ONA (6–12 IU BoNTA–ABO) per site is usually sufficient. Only 1–2 IU of onabotulinum toxin (2–4 IU of BoNTA-ABO) should be administered per location in the inferior pretarsal OO muscle. The risk of toxin diffusion into the orbit when injecting in the lateral canthal region rises with both proximity to the canthal angle and depth. Although a study specifically addressing this issue has not yet been conducted, it appears that injecting 1–1.5 cm from the lateral canthal angle reduces the possibility of the toxin's diffusion risk.[33]

Anecdotal reports offer several choices for brow injection placement, including straight into the tail of the brow, above the tail, and below the lateral brow. The location of the injection is probably not important if the toxin affects the OO muscle. The inferior side of the frontalis muscle should not be accidentally exposed to diffusion.[33]

To prevent unanticipated toxin diffusion into the levator muscle, some injectors who use a higher dilution (for example, 4 cm^3 of saline) and therefore a greater volume may be advised to inject proportionally more superiorly. Utilizing a stronger or less diluted injectable solution is an additional choice. According to some authors, a 1 cm^3 dilution provides incredibly accurate control over the treatment region. Always direct the needle away from the orbit since doing otherwise could cause toxin diffusion into the extraocular muscles or cause harm if the patient jerks suddenly while being injected. It is advised to perform very superficial intradermal injections, like a superficial bleb. When injecting the pretarsal OO muscle, extreme caution should be used. This muscle may be injected in two locations, corresponding to the medial and lateral corneoscleral limbi, or, it may be injected in the central region, just below the pupil. A dose of no more than 2 IU of BoNTA-ONA

should be administered initially if just one central injection is anticipated. At the 2-week follow-up appointment, more injections may be given if necessary. No more than 1.0–1.5 IU of BoNTA-ONA should be administered at each location if two separate ones are being used. Excessive toxin delivery in this area can hinder the closing of the eyelids and cause weeping, ectropion, and even the inward tilting of the eyelid (entropion). When the preseptal OO muscle contracts vigorously when the pretarsal muscle doesn't move, entropion may result. Pretarsal muscle and the edge of the eyelid are pushed inward toward the eye in this condition as the preseptal muscle advances upward, overriding it. Usually, this causes excruciating ocular discomfort and suffering. In order to prevent diffusion into the inferior oblique muscle, which is located relatively anteriorly in the orbit, it is best to administer lower eyelid injections subcutaneously. Vertical and/or torsional diplopia may occur if the inferior oblique is harmed.

The oblique lines, also known as "bunny lines," located above the nasal root and dorsum are the last treatment area of the upper face region. The nasalis' transverse part can constrict, causing bunny lines. This section protrudes from the maxilla and crosses the nose's bridge diagonally. A different cause of these lines, like the zygomaticus creating lateral canthal lines, is contraction of the levator labii superioris alequae nasi (LLSAN) in some cases.

In order to prevent the top lip from sagging, it is essential that injections stay away from the LLS. To reduce or get rid of these lines, one to three superficial injection spots in the nasalis muscle along the upper nasal sidewall and midline nasal dorsum should be sufficient. To get the required result, 1–3 IU of BoNTA-ONA (2–6 IU BoNTA-ABO) per injection location is usually enough.

Midface Treatment

There are few clinical studies on BoNTA used just for the midface. In the middle and lower parts of the face, the superficial and deep muscles that control facial expression are dependent on one another. These muscles are also close to some of the muscles around the mouth that are involved in speech articulation, mastication, and deglutition. However, rhytidectomy and other invasive procedures (such as different soft tissue suspension techniques) can produce better overall cosmetic results in many areas of the mid and lower face than soft tissue implants and fillers, while supplemental treatments with BoNTA injections can be used to enhance and prolong the final esthetic results.[32]

Nasal Tip Drop

Some people naturally twist their nasal tips downward as they get older, partially due to gravity and partially due to the hyperactive depressor septi nasi (DSN) muscle of the nasal septum. Recently, a non-invasive method to raise the nose tip and induce tip projection has been made available through BoNTA therapy. It's common to think of the DSN a component of the dilator naris. The depressor septi nasi narrows the nostril, draws the ala inferiorly, and pulls the nasal septum downward. Injections of BoNTA may be useful in elevating and projecting the nasal tip in people who can purposefully compress it downward by lowering their upper lip. In order to properly cure a fallen nasal tip, instruct the patient to push their upper lip downward, thereby enlarging the connection that exists between the base of the nasal columella and the upper lip. By lengthening the DSN, this maneuver separates the orbicularis oris from the DSN physically and functionally. This makes it possible to precisely inject the BoNTA into the DSN rather than into orbicularis oris fibers.

2–4 IU of BoNTA-ONA (4–8 IU BoNTA-ABO) can be injected just superior to this columella-labial junction, depending on the strength of the DSN. An additional 2–4 IU of BoNTA-ONA (4–8 IU BoNTA-ABO) may also be injected into the middle of the columella if the DSN is strong. Higher doses of BoNTA can be injected into stronger muscles. When treating a patient with an excessive upper gum smile, one of the muscles that may need to be decreased is the DSN.[34]

Exaggerated Upper Gum Smile

When they grin or laugh, some people have a propensity to expose an excessive quantity of their upper gum mucosa. This is sometimes perceived as a familial feature, which is particularly unsettling in women who exhibit this type of smile. According to calculations, the ideal tooth exposure when smiling is three-quarters of the height of the upper incisors' dental crowns, with no more than 1–2 mm of the mucosa showing. In general, men exhibit less interlabial excursion and gum than women. There are several causes for this "gingival smile," which develops when the interlabial area widens and the upper lip levators are overly contracted, exposing the gums excessively when you smile or laugh.[35,36] Other factors that may contribute to this situation include an excessively vertically long maxilla, a small upper lip that is inherited from one's parents, and a short crown length that may or may not be accompanied by an incisor alignment issue.

There are three grin patterns that can be used to identify someone, according to Rubin.[37,38] When the zygomaticus major controls the movement of the lips, it results in the first and most frequent type of grin (67% of the patients studied). This smile, known as the "Mona Lisa," starts with a sudden upward lift and outward pull of the corners of the mouth, followed by a gentle lift of the middle of the upper lip, exposing about 80% of the incisors. The pull of the zygomaticus major is mostly responsible for this type of smile. The second most frequent smile pattern (found in 35% of patients) is the canine smile, which is distinguished by a strong elevation of the upper lip's center, displaying the canine teeth first before the remainder of the upper lip is elevated. With a specific level of gingival exposure, the canine grin can result in anything from a minimal central dental reveal to a pronounced full denture show. This type of smile is primarily caused by the LLS muscle contracting and lifting the upper lip. A gummy smile happens when the LLS contracts strongly and severely. The third and least frequent grin type, which was observed in 2% of the individuals under study, is the complete denture smile. When the upper and lower lips separate at the same time, the upper and lower dentures may be partially or fully visible. This is known as a complete denture smile. This particular smile is the result of the coordinated contraction of the lower lip depressors and levators surrounding the mouth. The LLSAN contracts as the patient smiles. BoNTA-ONA (2-4 IU BoNTA-ABO) can be injected deeply intramuscularly and just above the periosteum at the point of maximum muscle thickness. Keep in mind to only use this injection technique on patients with a prominent gingival grin and palpable LLSAN. Avoid using the more laterally positioned muscles, such as the levator anguli oris, risorius, and the zygomaticus major and minor, as doing so could lead to either an adynamic or an unbalanced grin. Another method involves inserting the needle via the gingivolabial sulcus above the alveolar ridge at the same location in the nasofacial groove as previously mentioned and injecting 1–2 IU of BoNTA-ONA (2-4 IU of BoNTA-ABO) intraorally into the bellies of the two central upper lip levators. The central upper lip levators should only flimsily relax with a modest dose of low-volume BoNTA, preventing the top lip from entirely retracting upward. 1 IU of BoNTA-ONA (2 IU BoNTA-ONA) may need to be injected into the distal half of the DSN if the excessive gummy show is at its worst in the center of the upper lip.

Lower Face

Botulinum toxin treatment for the lower face is more difficult and unreliable than treatment for the upper face. The use of BoNTA in the lower face also increases the likelihood of undesirable results being produced. The lower face's architecture is intricate because the muscles there are closely spaced and interface at a number of distinct tiers and depths to carry out a variety of tasks, including speaking, eating, drinking, and facial expression.[26,39–42]

Orbicularis Oris Muscle

The orbicularis oris muscle is a large, elliptical muscle made up of concentric fibers that surround the mouth in a full ring.[43] This muscle causes the lips to close and protrude forward.[44] It is widely acknowledged that the orbicularis oris is divided into two pieces, an upper and a lower component, and is linked to the modiolus rather than being round. The muscle has two parts which vary in location and purpose: The pars marginalis and the pars peripheralis.

Pars marginalis: It extends as an arc under the free border of the lips in the two corners of the mouth, which are the points where the fibers of the superior and inferior parts of the muscle meet. The muscle's pars marginalis part functions as a sphincter.

Pars peripheralis: It is located in the cutaneous part of the lip, and in comparison to the pars marginalis, it is thinner. It is somewhat above the perioral muscles and rests in the mouth's most lateral corner. It serves as a dilator. Vertical fine perioral creases are accentuated by the contraction of this particular muscle.

A total of four injections are required, with two placed in the upper lip and two in the lower. The needle must only enter the skin for a distance of 2 mm during the brief subcutaneous injection. The correct location for the injection is in the center of each of the half lips.[45] Refrain from administering injections in the center of the upper lip. This lessens the possibility of a depression of the filtral crest. The injector should steer clear of treating the Cupid's arrow as well because this could cause the prominence's convexity to flatten. The injection of BoNTA orbicularis oris will lessen the appearance of fine vertical wrinkles, but it will have no impact whatsoever on the wrinkles that are the result of aging, primarily as a result of smoking habits.

To reduce the amount of toxin that diffuses into the surrounding tissues, administer 1 IU BONTA-ONA or 2.5 IU BoNTA-ABO per point.[39]

Mentalis Muscle

Three-dimensional muscle has fibers that go in a vertical direction from the cutaneous insertion, which is found superficially and inferiorly in the medial chin, to the lower deep origin in the mandible. The mentalis muscle fibers are directed medially downward, forming a central V-shaped triangle with the contralateral muscle that solely contains deep fat.[46] The lower lip is raised and protrudes thanks to the mentalis muscle. This muscle also contributes to the chin's skin's adhesion to the deeper layers such as subcutaneous tissue, giving the area a dimpling appearance. It creates a wrinkling effect on the chin as well as a "orange peel" look on the skin of the chin.

Injection technique: One injection point per side should be done. Each mentalis muscle receives an injection that is positioned 1 cm above the chin's tip and 5 mm laterally to the center line, right below the dimpled region. Before reaching the superficial skin insertion, the needle's tip penetrates the skin for 2–3 mm.

Dosage: 3 IU BoNTA-ONA or 7.5 IU BoNTA-ABO per side.[47]

Masseter Muscle

It is a thick muscle that is in the shape of a rectangle and connects the zygomatic bone to the ramus, mandibular angle, and coronoid process of the mandible. The pars superficialis and pars profunda make up the two muscle fibers that make up the masseter.[48,49] The superficial part of the muscle is a thick tendinous aponeurosis and is formed by the maxillary process of the zygomatic bone and the lower border of the zygomatic arch. Its fibers enter the mandible's angle and inferiolateral part of the ramus of the mandible by moving backward and downward. The middle and the inferior-posterior part of the zygomatic arch, and the deep layer of the deep temporal fascia make up the deep section of the muscle. The platysma muscle and the facial pedicle are the masseter's primary attachment points in the anterior and inferior regions; the parotid gland is its primary attachment point in the posterior region.

Technique for injection: Three injection locations are placed in the shape of a triangle, with two inferior points spaced around 1.5 cm apart and 0.5 cm above the inferior border of the mandible's body. The third (superior) point is placed 2 cm above the inferior points within the muscle mass.

The third point is located 2 cm above the earlier points within the muscle mass. Injections of BoNTA into this muscle lessen bruxism, lessen the muscle's appearance of hypertrophy, and reduce the magnitude of the angle formed by the mandible.

Dose: 8–40 IU BoNTA-ONA or 20–100 IU BoNTA-ABO per side.[47]

Platysma Muscle

On each side of the neck, the platysma muscle runs beneath the delicate subcutaneous tissue and is flat, broad, and thin. Its fibers stretch in an oblique direction upward and inward from the upper anterior thorax and the deltoideus muscle all the way down to the jaw and the oral commissure. The buccal commissures are laterally pulled downward by the platysma and DAO.[50]

The cervical platysma bands are created by the anterior platysma boundary.[51] Eight to ten injection locations are established on each side. The injections are administered in a vertical succession of locations in the posterior submandibular area and the anterior border of the muscle, into the platysma band, with an interval of 1–1.5 cm. The anterior border of the muscle is often narrow when the needle's tip enters the skin and subcutaneous tissue. Fingers are used to provide pressure to the front band, and then the needle tip is entered into a depth of 3–4 mm.[51] Because the platysma muscle is delicate and injections below the thyroid cartilage run the risk of the toxin spreading to the surrounding muscles, which could lead to dysphonia and/or dysphagia. Platysmal bands will relax as a result of botulinum toxin injections in this muscle, which will also make the mandibular line seem better and reduce the horizontal lines that appear on the neck.[52]

Dose: 20–50 IU BoNTA-ONA or 50–125 IU BoNTA-ABO per side.[53]

Primary Focal Hyperhidrosis

Multiple injections of the toxin into the hyperhidrotic area resulted in a regionalized reduction in cholinergic transmission, which remained stable over time but could be reversed. Eccrine glands are good targets for BoNTA because they receive their innervation from postganglionic fibers that are sympathetic cholinergic. BoNTA is currently only used for the treatment of localized hyperhidrosis by intradermal injections.

Axillary Hyperhidrosis

BoNTA treatment in this area typically lasts 4–10 months, while some trials have shown that it can work for up to 14 months.[54–57] Repeated BTX-A injections produce symptom relief that lasts for about the same amount of time, indicating that patients do not acquire treatment resistance.[54] Typically, anhidrosis sets in 7 to 10 days after receiving a BoNTA injection. A number of Quality of Life (QOL) indicators have dramatically improved along with the reduction in sweating symptoms. In addition to being equally effective, subcutaneous injections may also be more comfortable.[58]

Table 4. Microdroplets BoNTA dilution[66]

Neurotoxin	Dilution
BoNTA-ONA	100 U in 10 mL normal saline, 1 unit = 0.25 mL
	100 U in 5 mL normal saline, 1 unit = 0.5 mL
	100 U in 2.5 mL normal saline, 1 unit = 0.1 mL (dose used as per area injected)
BoNTA-ABO	500 U in 2.5 mL saline 70 units/mL (0.35 mL) further diluted in 0.65 mL

Table 5. Doses of microdroplets BoNTA[66]

Region	Differing techniques
Forehead	24–28 U (0.6–0.7 mL of standard dilution ONA in 1 mL saline)-single syringe[71]
	OR
	8–20 microdroplets of 0.5–1.5 U each[71]
Periorbital	Under eye–8–12 U (0.2–0.3 mL of standard dilution ONA in 1 mL saline)[72]
	Lateral canthal lines–1–5 microdroplets of 1–4 U each[71]
Midface	20 U (0.5 mL of standard dilution ONA in 1 mL saline) – single syringe[72]
Lower face Jawline and neck	Jawline and neck – 24 U (0.6 mL of standard dilution ONA in 1 mL saline)-two syringes.

Injection patterns can be random or radial, starting at the edge of the skin that bears hair and spiraling inside or outward toward the center of the axillary vault (or vice versa).[59] For each axilla, 50–100 IU of BoNTA-ONA in 10–20 intradermal injections of 0.1–0.2mL aliquots should be utilized, depending on the surface area.[60,61]

Palmar and Plantar Hyperhidrosis

The usual duration of anhidrosis with therapy is 4–12 months, which is less than the duration of axillary hyperhidrosis.[62] The main side effect of BTX for palmar hyperhidrosis is transient weakening of the intrinsic hand muscles. In 45–77% of treated patients, the weakness develops, usually starts within 3 days, and goes away in 10–14 days.[63] The majority of patients have normal, quantitatively determined handgrip strength, but frequently have decreased finger pinch strength. BoNTA may not penetrate deeply enough to impact intrinsic muscle activity if injections are precisely placed high up in the dermis.[64] Due to the numerous injections made into the palm throughout the operation, severe discomfort and soreness are also felt, which makes this therapy challenging to tolerate.[63]

Few studies have looked at BoNTA treatment for plantar hyperhidrosis because intradermal injections are difficult because of the thicker stratum corneum on the soles of the feet.[61] Uncontrolled investigations have revealed that BoNTA treatment for plantar hyperhidrosis may be equally successful as for palmar hyperhidrosis, requiring comparable dosages and producing symptom alleviation and better QOL for about 6 months.[57]

The eccrine glands are located at the intersection of the dermis and subcutaneous tissue, which indicates the appropriate depth of injection in this area. For each palm or sole, approximately 40–50 injections of 0.05–0.1 mL aliquots separated by 1–1.5 cm should be utilized, frequently containing 100–240 IU of BoNTA-ONA, depending on the surface area.[61] Because perpendicular injections might cause substantial backflow from the injection canal, the needle should be positioned at an oblique angle.[61]

Craniofacial Hyperhidrosis

The injections of 2–4 IU of BoNTA-ONA placed approximately every two cm can be used to treat craniofacial hyperhidrosis in several areas of the face, including the upper third of the skin on the forehead, the frontal hairline, and 2 cm beneath the anterior hairline.[59] To keep sweating under acceptable limits, patients with craniofacial hyperhidrosis often need injections every 5–6 months.[65]

Microdroplet Botulinum Toxin

Over the past 20 years, botulinum toxin type A (BoNT) has increasingly been used off-label through the use of microbotox, mesobotox, or the microdroplet approach.[66] In the original method, BoNTA-ONA was administered as equally spaced intradermal microdroplets.[67,68] Although BoNTA-ONA was utilized when the approach was first applied, different varieties of BoNT have since been employed.[69] The objective is to reduce fine lines and wrinkles without giving the face a frozen or synthetic appearance.[70] Microdroplet BoNTA affects the face muscles' superficial

fibers, which are connected to the lower dermis. It can help with seborrhea and facial hyperhidrosis in addition to all these other effects.[70] Table 4 lists the BoNTA dilution rates for the application of microbotox.[66]

A 30–32 G needle with a bevel that is directed downward and nearly parallel to the skin is used for the method. The plunger is gently pressed, which is just enough to cause a little bleb to rise.[71] An intradermal delivery is indicated by resistance on the plunger, whereas an erroneous, deep placement of the fluid is indicated by an easy flow. In an even, grid-like pattern, 0.05 mL of the solution is intradermally injected at 1 cm intervals.[68]

For those who want an eyebrow lift without a motionless forehead, microdroplet BoNTA is advised for use on the upper face. Experienced injectors should deal with the midface and under-eye region because improper solution placement and excessive droplet size might cause diffusion to deeper muscle fibers and adverse effects.[71] With its application to the lower face, the platysma's superficial fibers and lower face depressors are relaxed, resulting in a defined cervicomental angle and a sharper jawline, giving a small neck lift.[67] For the lower face and neck, some experts suggested combining the microdroplet approach with traditional BoNTA for greater benefits. The platysmal bands and masseter are debulked by traditional BoNTA, but the skin around the neck is tightened by the microdroplet technique, especially in patients with thin horizontal necklines and crepe-like skin.[67] The dosages are listed in Table 5.[66]

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