Review article

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BEYOND THE GLABELLA: EMERGING AESTHETIC APPLICATIONS OF BOTULINUM TOXIN TYPE A IN THE MODERN FACIAL REJUVENATION ERA

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Abstract

Botulinum toxin type A (BoNT-A) remains the most common minimally invasive aesthetic procedure performed worldwide, yet the original glabellar indication now accounts for only a small fraction of routine practice. This narrative review examines the current state of aesthetic BoNT-A applications in 2026, covering new formulations, intradermal microdroplet techniques, lower-face contouring approaches, treatment of skin-quality concerns, combination protocols, and emerging immunogenicity considerations. We searched PubMed, Embase, and Web of Science for English-language trials, systematic reviews, and consensus statements from 2010 through early 2026, prioritizing publications from the past five years. Peptide-stabilized daxibotulinumtoxinA, prabotulinumtoxinA, and letibotulinumtoxinA have ended the long-standing Botox–Dysport–Xeomin monopoly and renewed the focus on product-specific dosing considerations. Microbotox

protocols now routinely address pore size, sebum production, fine wrinkles, and erythema, with significantly less impact on facial expression. Advanced techniques, including masseter contouring, the Nefertiti lift, gummy-smile correction, and platysmal-band treatment, have transitioned from experimental procedures to routine clinical practice. The dominant treatment paradigm has shifted toward combination protocols that integrate BoNT-A with hyaluronic acid fillers, biostimulators, and energy-based devices, as reflected in most current consensus statements. BoNT-A is no longer simply a single-indication wrinkle relaxant but has become a versatile tool for comprehensive facial rejuvenation. Future priorities include head-to-head comparative trials, harmonized dosing protocols for newer products, and long-term immunogenicity surveillance data.

Key words: botulinum toxin type A, facial rejuvenation, microbotox, daxibotulinumtoxinA, aesthetic medicine, off-label

Pregledni rad

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Izvan glabele: nova estetska primena botulinum toksina tip A u eri savremenog facijalnog pomlađivanja

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Sažetak

Botulinum toksin tip A (BoNT-A) ostaje najčešća minimalno invazivna estetska procedura koja se izvodi širom sveta, ipak originalna indikacija za glabelu sada čini samo mali deo rutinske prakse. Ovaj narativni pregled razmatra trenutno stanje estetskih primena BoNT-A u 2026. godini, pokrivajući nove formulacije, intradermalne tehnike mikrokapi, pristupe konturisanju donjeg dela lica, tretman problema kvaliteta kože, kombinovane protokole i nova razmatranja imunogenosti. Pretražili smo PubMed, Embase i Web of Science za studije na engleskom jeziku, sistematske preglede i konsenzus izjave od 2010. do početka 2026. godine, dajući prioritet publikacijama iz poslednjih pet godina. Peptidno stabilizovani daxibotulinumtoksinA, prabotulinumtoksinA i letibotulinumtoksinA završili su dugogodišnji monopol Botox–Dysport–Xeomin i obnovili fokus na specifična razmatranja doziranja proizvoda. Mikrobotoks protokoli sada rutinski rešavaju veličinu pora, produkciju sebuma, fine bore i eritem, sa značajno manjim uticajem na facijalnu ekspresiju.

Napredne tehnike, uključujući konturisanje masetera, Nefertiti lift, korekciju gummy smile-a i tretman platizmalnih traka, prešle su iz eksperimentalnih u rutinsku kliničku praksu. Dominantna paradigma tretmana se pomerila ka kombinovanim protokolima koji integrišu BoNT-A sa hijaluronskim filerima, biostimuatorima i uređajima zasnovano na energiji, što se odražava u većini trenutnih konsenzus izjava. BoNT-A više nije jednostavan relaksant bora jedne indikacije već svestran alat za sveobuhvatno facijalno pomlađivanje. Budući prioriteti uključuju direktno poredne studije, harmonizovane protokole doziranja za novije proizvode i dugotrajne podatke o nadzoru imunogenosti.

Ključne reči: botulinum toksin tip A; facijalno pomlađivanje; mikrobotoks; daxibotulinumtoksinA; estetska medicina; off-label.

Introduction

Botulinum toxin type A (BoNT-A) is a presynaptic neurotoxin produced by Clostridium botulinum. It cleaves SNAP-25, a component of the SNARE complex required for vesicle fusion, thereby blocking acetylcholine release at the neuromuscular junction. The resulting muscle relaxation is temporary and reversible, forming the pharmacological basis for all approved aesthetic indications. OnabotulinumtoxinA received FDA approval for glabellar lines in 2002, and since then, the product class has remained at the top of every global registry of nonsurgical cosmetic procedures, with several million treatments delivered each year (1,2).

Two things have changed the field over the past ten years. The first is the pharmacology. Onabotulinumtoxin A, abobotulinumtoxin A, and incobotulinumtoxin A are no longer the only options; prabotulinumtoxin A, letibotulinumtoxin A, and the peptide-stabilized daxibotulinumtoxin A have all reached international markets, each with its own excipient chemistry and duration profile (3,4). The second is the anatomical distribution of injections in clinical practice. Treatment has shifted from the upper third of the face to the entire face and neck, and from a straightforward intramuscular technique to intradermal microdroplet work targeting the dermis rather than the underlying muscle (5,6).

The role of an aesthetic neuromodulator has expanded accordingly. BoNT-A is now used to refine facial proportions, reshape the jawline, lift the brow and corners of the mouth, control sweating and seborrhea, reduce rosacea-related erythema, and improve the quality of surgical scars. The patient population has also shifted. A growing share of treatments is performed on patients under 35, the so-called preventive cohort. Patients over 65 are now common in comprehensive rejuvenation programs. Men account for more than 10% of cosmetic neuromodulator procedures in many large practices (1,2).

This review synthesizes the clinically relevant aspects of these developments, focusing on evidence from the past five years. It is organized around five themes: new BoNT-A formulations and what they deliver; the intradermal microdroplet technique and skin quality; lower-face and neck contouring; dermatologic and quasi-medical applications; and combination protocols. Safety, immunogenicity, and the field's apparent direction are addressed separately at the end. The intended reader is the practicing injector who has been performing glabellar and forehead treatments for years and seeks a current perspective on the broader range of BoNT-A applications. When published data are limited, that is stated plainly. When a technique is effective, the practical

parameters – dose ranges, dilutions, injection depth, common pitfalls – are provided in sufficient detail to be useful in clinical practice. None of this replaces hands-on training under a competent mentor, which remains the only reliable way to learn these techniques.

Pharmacologic Evolution: New Botulinum Toxin Type A Formulations

Daxibotulinumtoxin A

The FDA approved DaxibotulinumtoxinA-lanm (Daxxify®, Revance Therapeutics) in September 2022 for the treatment of moderate-to-severe glabellar lines. Structurally, the product is unusual. The 150-kDa core neurotoxin is stabilized by RTP004, a proprietary 35-amino-acid, positively charged peptide that replaces human serum albumin. Two consequences follow: the formulation contains no human-derived components, and the duration of clinical effect is longer than that observed with conventional preparations (7,8). The pivotal SAKURA Phase 3 trials reported a median time to loss of effect of about 24 weeks for glabellar lines. A subset of patients still had a satisfactory response at nine months, roughly twice the duration of standard formulations (9). A subsequent open-label Phase 2 study extended the product to the rest of the upper face and showed that a single three-region session covering the glabella, frontalis, and lateral canthal lines maintained efficacy across all three sites (10). Real-world experience with the frontalis suggests that spreading the dose over a wider treatment area with more injection points allows the injector to use 20–33% fewer units while preserving duration compared with the older four-point pattern (11).

PrabotulinumtoxinA

PrabotulinumtoxinA (Jeuveau®, Nabota®) is derived from the Clostridium botulinum Hall-A strain and is approved for glabellar lines in the United States, South Korea, and several European markets. Phase 3 non-inferiority data compared with onabotulinumtoxinA showed comparable efficacy and safety, with an onset at 3–4 days and duration of about 12 weeks (12). A smaller comparative study of upper-face expression lines found that prabotulinumtoxinA may act slightly faster during the first three to seven days, but the difference disappears by the end of the first month (13). In the lateral canthal region, a head-to-head comparison with onabotulinumtoxinA showed no meaningful difference in peak effect or duration (14).

LetibotulinumtoxinA

LetibotulinumtoxinA was developed in South Korea, dominates much of the Asian market, and is entering the European market. A consensus on aesthetic use in Asian patients supports conservative per-site dosing (2–4 units) and retreatment at six to twelve months to maintain a natural result (15). Head-to-head comparative trials remain scarce. A 2024 Thai multi-product study evaluated five formulations – incobotulinumtoxinA, onabotulinumtoxinA, abobotulinumtoxinA, letibotulinumtoxinA, and prabotulinumtoxinA – for masseter reduction and upper-face wrinkles. The five products showed broadly similar onset and peak-effect kinetics; bite-force reduction peaked between weeks two and four in all groups (16).

Implications for Dose Conversion

Empirical conversion ratios are popular for one reason: they are convenient. Modern pharmacodynamic modeling argues that they are also potentially unreliable. A recent in silico analysis aggregated data from 49 clinical trials and regulatory submissions across six FDA-approved formulations and simulated each formulation in 10.000 virtual patients. The between-product variability in EC50, peak efficacy, and decay rate was real and clinically meaningful (17). The practical message is simple. Each product should be dosed according to its own evidence base, not a universal conversion factor. The familiar 1:2.5–1:3 onabotulinumtoxinA-to-abobotulinumtoxinA ratio is still used in the clinic, but there is no reason to expect it to translate to the newer products, particularly DAXI, whose peptide-stabilized 150-kDa core has nothing in common with the 900-kDa complex of the older formulations. Clinics stocking multiple products do better with product-specific injection maps and unit ranges per anatomic site. For new patients, sticking with the same product across the first two cycles is the most reliable way to learn individual response.

Table 1. Comparison of clinically relevant botulinum toxin type A formulations used in aesthetic medicine.

Product (INN / brand)	Manufacturer	Complex size (kDa)	Stabilizing excipient	FDA glabellar approval	Reported median duration (glabella)
OnabotulinumtoxinA (Botox® Cosmetic)	AbbVie / Allergan Aesthetics	900	Human serum albumin	2002	3–4 months
AbobotulinumtoxinA (Dysport®)	Galderma / Ipsen	500–900	Human serum albumin, lactose	2009	3–4 months
IncobotulinumtoxinA (Xeomin®)	Merz Aesthetics	150 (naked)	Human serum albumin, sucrose	2011	3–4 months
PrabotulinumtoxinA (Jeuveau®, Nabota®)	Evolus / Daewoong	900	Human serum albumin	2019	3–4 months
DaxibotulinumtoxinA (Daxxify®)	Revance Therapeutics	150 + RTP004 peptide	RTP004 (35-aa peptide); albumin-free	2022	~6 months (up to 9)
LetibotulinumtoxinA (Botulax®, Letybo®)	Hugel / Croma	900	Human serum albumin	2024	3–4 months

INN, international nonproprietary name; aa, amino acid; kDa, kilodalton. Approval years refer to United States Food and Drug Administration (FDA) approval for moderate-to-severe glabellar lines. Duration ranges are based on pivotal Phase 3 data and product labeling and may vary according to anatomical site, dose, and individual patient factors.

Foundational Upper-Face Techniques in the Modern Era

Although this review focuses on new applications, no honest discussion of contemporary practice can overlook the upper face. The five-point glabellar pattern (two injections into each corrugator supercilii plus one into the procerus) remains the default in most teaching programs, but a 2024 Korean expert consensus recommended alternative patterns based on age, sex, and the degree of muscle movement (18). Younger women with mild lines and weaker corrugators tend to do well with a three-point approach and lower total doses, typically around 10–15 units of onabotulinumtoxinA-equivalent. This approach preserves a little medial brow movement and avoids the overly immobile appearance that has come to identify dated technique. Older patients

with deep static lines and most men need the full five-point pattern and 20–30 units simply because the depressor complex is more prominent and stronger (18).

Frontalis injection has also evolved. The old uniform, symmetric eight-point pattern has largely been replaced by an individualized approach guided by where the patient's frontalis actually contracts. The active muscle is often asymmetric and rarely spans the full width of the forehead. Two principles dominate modern technique: stay 1.5–2 cm above the supraorbital rim and start conservatively with a planned two-week review. Real-world DAXI data make the same point in a different way — a wider field with more points but fewer total units maintains duration while reducing brow heaviness (11). The lesson generalizes across products. Dosing distributed across more points within the active muscle envelope yields more natural and reproducible results than dosing concentrated at a few high-volume sites.

Lateral canthal lines (crow's feet) are typically treated with three points lateral to the orbital rim, with the most superior point placed about 1 cm above the lateral canthus and additional points 1–1.5 cm apart along the lateral orbicularis oculi. Doses range from 8 to 15 units per side, depending on muscle bulk, line depth, and the product chosen. A well-known refinement is a single intradermal injection into the inferior pretarsal orbicularis oculi to widen the eye aperture – the “eye-opening” technique, particularly popular in Asian practice. It is not for everyone. Patients with poor orbicularis tone may develop undesirable lower eyelid weakness and should be selected carefully.

Brow shaping and the chemical brow lift

The chemical brow lift works by selectively weakening the brow depressors – lateral orbicularis oculi, corrugator, procerus, and depressor supercilii – allowing the unopposed frontalis to elevate the brow. The effect is primarily lateral. Small doses of 2–4 units of onabotulinumtoxinA-equivalent into the lateral orbicularis oculi can elevate the brow tail by 1–3 mm in suitable candidates (19,20). Earlier protocols described a 5-unit glabellar injection paired with four equally spaced injections along the lateral orbital rim. This produced statistically significant elevations at all three measurement points – nasal, central, and temporal regions of the brow (21). More recent anatomically driven techniques, such as the Moose technique, have shifted the conversation upstream. The argument is that thorough pre-assessment of facial expression – anger, sadness, surprise, neutrality – combined with patient-engaged mirror simulation before any injection, reduces the rate of asymmetry and the Mephisto sign (the lateral peak in a quizzical configuration)

(22). The contraindication that catches even experienced injectors is compensated brow ptosis. If a patient's brow is elevated solely because the frontalis is contracting continuously, paralyzing the frontalis will allow the brow to fall onto the upper lid.

Table 2. Suggested unit ranges for selected upper-face and lower-face indications using onabotulinumtoxinA-equivalent doses.

Anatomical region / indication	Target muscle(s)	Typical dose per side / total (U)	Key technical considerations
Glabellar lines	Corrugator supercilii, procerus, depressor supercilii	20–30 total (3- or 5-point pattern)	Higher doses for males and deep static lines; spare medial fibres in delicate cases
Forehead lines	Frontalis	8–20 total	Avoid injection within 1.5–2 cm of supraorbital rim; respect lateral muscle extent
Lateral canthal lines (crow's feet)	Orbicularis oculi (lateral)	8–15 per side	3-point pattern lateral to orbital rim; conservative dose to avoid lower-lid weakness
Chemical brow lift (lateral)	Orbicularis oculi (lateral fibres)	2–4 per side	Small superficial dose; risk of Mephisto sign with overcorrection
Bunny lines	Nasalis (transverse)	2–5 per side	Single midline-lateral injection; avoid levator labii alaeque nasi
Gummy smile	LLSAN ± LLS, zygomaticus minor	2–5 per side (Yonsei point)	Conservative dosing; over-correction produces upper-lip lengthening and dental show loss
Perioral rhytides	Orbicularis oris (superficial)	2–4 total	Very conservative; risk of oral incompetence and articulation difficulty in singers/wind musicians
Marionette / DAO	Depressor anguli oris	2–5 per side	Inject low and lateral on mandibular border to spare depressor labii inferioris
Mentalis (peau d'orange)	Mentalis	4–10 total (1–2 midline points)	Single deep injection near pogonion; avoid superficial spread to lower lip depressors
Masseter contouring	Masseter (deep belly)	20–40 per side (3–4 points)	Inject within safe-zone triangle; pinch-and-inject to confirm muscle depth
Nefertiti lift / platysmal bands	Platysma (vertical bands and inferior mandibular border)	15–30 total (multi-point)	Best in younger patients with elastic skin and prominent platysmal hyperactivity

U, units of onabotulinumtoxinA-equivalent; LLSAN, levator labii superioris alaeque nasi; LLS, levator labii superioris; DAO, depressor anguli oris. Doses are illustrative ranges intended to support clinical decision-making and must be individualized based on patient anatomy, muscle

activity, prior treatment response, and product-specific dosing data. Off-label indications should be discussed and documented as part of informed consent in the relevant jurisdictions.

Microbotox and Mesobotox: Intradermal Microdroplet Techniques

Concept and Rationale

Microbotox – also called mesobotox, microtoxin, or intradermal microdroplet injection – was popularized by Wu and has since become one of the most discussed innovations in aesthetic neuromodulation. The idea is to avoid the belly of the mimetic muscle and instead deliver many small aliquots of highly diluted BoNT-A into the superficial dermis or the dermis–superficial muscle interface. The pharmacological targets differ: cutaneous cholinergic receptors on sebaceous glands, eccrine glands, and arrector pili muscles, as well as fine fibers of the superficial musculo-aponeurotic system that contribute to dermal-level creasing (5,23).

Two factors make this clinically attractive. First, the deep mimetic musculature is left intact, preserving facial expression – an increasingly explicit demand among younger, more sophisticated patients who refuse the “frozen” appearance. Second, the range of treatable concerns is broad. Enlarged pores, seborrhea, fine textural rhytides, mild skin laxity, and persistent erythema are all conditions for which conventional intramuscular BoNT-A has no effect (24). The anatomical basis is reasonably well established. Eccrine and sebaceous glands in facial skin express both nicotinic and muscarinic acetylcholine receptors, providing a plausible target for cholinergic blockade independent of the neuromuscular junction. The cutaneous pilomotor muscles, which contribute to follicular ostium prominence under sympathetic drive, also respond to local BoNT-A. This combined action likely explains the reductions in pore visibility, sebum output, and surface oiliness observed in clinical practice.

Dilutions, Injection Patterns, and Practical Protocols

Published microbotox protocols vary widely in dilution, total dose, and injection density. A 2022 systematic review included twenty studies using onabotulinumtoxinA, abobotulinumtoxinA, or incobotulinumtoxinA. The most common concentration was 10–20 U/mL of onabotulinumtoxinA-equivalent. Injection points ranged from as few as four (forehead and periorbital regions only) to as many as 999 across the whole face, with inter-point spacing between 2 mm and 2 cm (5). A later prospective randomized study compared three onabotulinumtoxinA dilutions – 1:5, 1:7, and

1:10 in saline – for periorbital and mid-facial rejuvenation. The more concentrated 1:5 preparation produced significantly higher Global Aesthetic Improvement Scale scores at one and six months than the more dilute formulations (25). The implication is less intuitive for the standard 'just dilute it more to be safe' approach: intradermal efficacy is at least partly concentration-dependent.

An expert roundtable on intradermal microdroplet practice emphasized two key points: patient selection and meticulous injection technique. The right candidates are those with enlarged pores, mild skin laxity, oily skin or seborrhea, and acne-related textural irregularity. Depth is always in the superficial dermis. Microdroplets are placed roughly 5–10 mm apart, depending on the region and the chosen concentration (24).

Pore Size, Sebum Control, and Skin Quality

A 2024 systematic review and meta-analysis pooled data from thirteen clinical trials of intradermal BoNT-A and concluded that the technique reliably improves sebum production, pore size, erythema index, fine wrinkles, skin texture, and overall facial rejuvenation effect. Data on skin hydration were inconsistent, and the evidence base did not yet meet the thresholds for definitive conclusions under trial-sequential analysis (26). The mechanism of sebum reduction is thought to involve the interruption of acetylcholine signaling via non-neuronal cholinergic receptors on sebaceous gland cells, with downstream effects on sebocyte differentiation and lipogenesis (27).

Pore size and skin texture appear to be dose- and concentration-dependent within practical limits. The randomized trial comparing 1:5, 1:7, and 1:10 dilutions (27) underscores that pharmacologically active concentrations are needed for a meaningful cutaneous response. Heavy dilution reduces the risk of unintended muscle weakness but also diminishes clinical efficacy proportionally. The implication for protocol design is that concentration should be matched to the objective. Use the more concentrated 1:5 preparation when pore reduction and sebum control are the goals. Use the more dilute 1:7 to 1:10 dilutions when treating large surface areas such as the neck or décolleté, where the total dose must be capped.

Acne-related pore enlargement has emerged as a particularly responsive indication. A 2025 retrospective analysis treated forty patients with acne with intradermal BoNT-A plus non-cross-linked hyaluronic acid delivered via a 32-gauge nine-needle mesotherapy device (mesogun). VISIA-quantified pore counts, skin texture, and porphyrin scores improved at one month, with a smaller but still measurable benefit at four months (28). A separate split-face randomized

comparison of intradermal BoNT-A against saline ruled out the obvious confounder: pore-size reduction is a real pharmacologic effect, not an artifact of needle-induced microtrauma (29).

Adverse Events and Patient Selection

Microbotox is generally safe, but it has a distinct complication profile, and patients require explicit pre-treatment counseling. The main clinical concern is unintended deep diffusion into mimetic muscles when injection volumes are large or when the needle inadvertently passes through the dermis into the underlying muscle belly. In the lower face, this can cause transient smile asymmetry or lower-lip weakness. In the periorbital region, it can cause brow ptosis or upper-eyelid heaviness. Bruising is also more common than with conventional intramuscular technique because of the many injection points, each of which can injure a small dermal vessel. Patients should stop nonessential anticoagulant supplements and avoid alcohol for 24–48 hours before treatment. Pinpoint erythema and edema usually resolve within hours, but in reactive skin, they can last up to one to two days. Severe skin laxity, established jowling, and Glogau type IV photoaging are not indications for microbotox; these patients need combination protocols involving fillers, biostimulators, or surgical lifting.

Lower Face and Neck Contouring

Masseter Reduction

Masseter hypertrophy is the most established off-label indication for BoNT-A, particularly in Asian aesthetic practice, where reducing a square or wide lower-face contour is a common request. Bilateral injection of 20–40 units of onabotulinumtoxin A-equivalent into three or four points within the safe zone of each masseter belly produces visible volume reduction within four to eight weeks. Peak slimming occurs at three months, and many patients continue to see benefits beyond six months (30,31). Long-term volumetric studies have documented muscle-volume reductions of about 12% with maintenance protocols (30).

The classical safe zone is an inverted triangle bounded superiorly by a line from the tragus to the oral commissure, inferiorly by the inferior border of the mandible, and anteriorly by the anterior border of the masseter. This triangle protects against inadvertent involvement of the risorius and zygomaticus major and reduces the risk of paradoxical smile asymmetry. The injection depth must reach the deep belly. Overly superficial injection results in inadequate slimming and

increases the risk of diffusion into adjacent muscles. Common adverse events include transient masticatory weakness in the first two weeks, mild paradoxical bulging during hard biting in the early post-injection period, and, in rare cases, asymmetric or inverted smile when toxin spreads anteriorly. Combining masseter BoNT-A with chin or jawline filler – or, in selected cases, autologous fat grafting – addresses both the contraction and volumetric components of lower-face shaping (30).

Patient selection deserves more attention than it usually receives. Not every wide lower face is due to masseter hypertrophy. A wide mandibular angle, prominent buccal fat pads, parotid enlargement, and submandibular gland prominence all produce a similar visual impression and are not improved by masseter BoNT-A. The simplest clinical test is to ask the patient to clench. A true masseter that responds well to BoNT-A is firm, palpably contracted, and visibly bulges on clenching. If the lower-face width is the same at rest and on clench, the masseter is not the dominant contributor, and the patient should be redirected to filler, fat removal, or surgical alternatives. Another point to raise at the consultation is the risk of accelerated buccal fat pad hollowing. In patients with low subcutaneous facial fat to begin with, sustained masseter reduction can unmask a thin, gaunt lower face that the patient did not anticipate. A pre-treatment photograph at rest and smiling, combined with a candid discussion of what the lower face will look like in six months' time, prevents the unhappy patient from returning with a complaint that the treatment has "aged" them.

The Nefertiti Lift and Platysmal Bands

The Nefertiti lift – named after the Egyptian queen's elegantly defined jawline – targets both vertical platysmal banding and the downward pull of the platysma on the inferior mandibular border. The technique uses a series of small injections along the inferior mandibular margin, combined with intramuscular injections into prominent platysmal bands, using either onabotulinumtoxin A or abobotulinumtoxin A at conservative per-point doses (32). Clinical evaluation using validated photometric scales for jowls, marionette lines, oral commissures, neck volume, and platysmal band severity demonstrates measurable improvement. The effect is strongest in younger patients who still have platysmal hyperactivity and good skin elasticity (32). Older patients with established jowling and substantial cervicofacial laxity constitute a different population. They are better served by surgical or device-based interventions.

Gummy Smile

Excessive gingival display on smiling – usually defined as more than three millimeters of visible gingiva – is one of the more aesthetically distressing complaints and is among the most reliably responsive to BoNT-A. The injection targets the levator labii superioris alaeque nasi (LLSAN), sometimes also the levator labii superioris (LLS) and zygomaticus minor. The Yonsei point is the standard anatomic landmark: a single injection site that targets all three elevators of the upper lip at once (33). A 2024 systematic review and bibliometric analysis confirmed that the muscles most commonly injected are LLSAN, LLS, zygomaticus major and minor, and orbicularis oris. Cumulative doses of 2–7.5 units of onabotulinumtoxin A per side produce satisfactory results in most published series (34,35). Effect duration is typically three to four months, and retreatment intervals can usually be extended once the patient learns to modulate their smile dynamics.

Perioral Rejuvenation

Perioral rhytides – the so-called smoker's lines or barcode lines – result from chronic contraction of the orbicularis oris superimposed on age-related dermal thinning and volume loss. Conservative intramuscular injection of 2–4 units of onabotulinumtoxin A-equivalent at two or four superficial points along the upper and lower vermilion borders softens these lines without causing oral incompetence or articulation difficulty. A few practical points are worth keeping in mind. Avoid the corner of the mouth: diffusion to the risorius and depressor anguli oris can produce smile asymmetry. Be cautious in patients who depend professionally on lip dexterity – singers, wind musicians, and voice actors. And recognize the limits of the technique. BoNT-A alone rarely provides satisfactory correction of deep static perioral lines. Filler, fractional resurfacing, or biostimulator injection is usually needed as an adjunct. Patients should be told that they will experience temporary, mild lip flattening and that articulation of plosive consonants ('p', 'b') may feel subtly altered for one to two weeks.

Depressor anguli oris (DAO) injection is one of the most underused yet highest-yielding lower-face techniques. It elevates downturned oral commissures. The DAO originates from the inferior mandibular border and inserts into the modiolus, pulling the corner of the mouth downward. Injecting 2–5 units per side, placed low and slightly lateral on the mandibular border to avoid diffusion into the depressor labii inferioris, releases this downward vector. The unopposed elevators (zygomaticus major and minor, levator anguli oris) can then lift the commissure into a neutral or subtly elevated position. The effect is usually subtle but cumulative. Patients often

describe feeling that they "look less sad" rather than that they "look younger"– a distinction worth discussing in consultation so expectations match what the procedure actually delivers (30).

Chin and Mentolabial Region

The mentalis is a paired conical muscle that originates from the mandibular alveolar bone and inserts into the chin dermis. When it is hyperactive, the result is a cobblestone or peau d'orange chin, an accentuated mentolabial sulcus, and sometimes lower-lip eversion or strain during speech and swallowing. Injection of 4–10 units of onabotulinumtoxin A-equivalent into one or two midline points high on the chin pad, near the bony pogonion, relaxes the muscle while preserving its functional role in lip support (30,36). The most common pitfall is superficial injection or migration to the depressor labii inferioris, which produces temporary lower-lip weakness with drooling, particularly noticeable during lateral lip movement. Pairing chin BoNT-A with chin filler addresses both components of the problem – the dynamic dimpling component is handled by the toxin, and the volumetric component by the filler. This combination is now the standard of care for comprehensive lower-face rejuvenation.

Bunny lines are the diagonal rhytides that appear on the dorsum of the nose during smiling or sneering. They are produced by the transverse fibers of the nasalis. Two to five units placed superficially on the lateral aspect of the nasal sidewall, medial to the nasofacial groove, soften the lines without compromising nasal airflow. The trap is the levator labii superioris alaeque nasi. Injecting too close to the nasolabial fold engages that muscle and produces upper-lip ptosis – an embarrassing complication that is best avoided by careful attention to anatomical landmarks rather than corrected after the fact.

Skin-Quality and Dermatologic Indications

Erythematotelangiectatic Rosacea

Persistent facial erythema and flushing in erythematotelangiectatic rosacea (ETR) previously lacked satisfactory pharmacologic treatment. Intradermal microdroplet BoNT-A has emerged as a promising adjunct. The presumed mechanism is inhibition of acetylcholine-mediated cutaneous vasodilation, along with modulation of mast cell-derived neuropeptide release (37,38). Early clinical series reported reductions in flushing, erythema, and inflammation within a week of treatment, with effects lasting up to three months (38). The strongest evidence to date is a

randomized, double-masked, split-face Phase IV study of intradermal BoNT-A versus saline placebo in thirty ETR patients. The outcomes – clinician erythema assessment, patient self-assessment, erythema index, dermoscopy, and capillaroscopy – all moved in the same direction, confirming that the effect is reproducible and quantifiable (37). Working protocols typically use heavily diluted onabotulinumtoxin A (1:7 to 1:10 in saline) injected as 0.05–0.1 mL aliquots into the cheeks, with total per-side doses of 8–12 units. One important caveat: BoNT-A controls the erythematous and flushing components of rosacea but does very little for telangiectasia or papulopustular lesions. Vascular lasers, intense pulsed light, and topical or oral antibiotics still address that domain. BoNT-A should be considered one component of a multimodal rosacea regimen, not a stand-alone therapy.

Acne and Seborrhea

Cholinergic regulation of sebocyte function underlies the rationale for intradermal BoNT-A in oily skin and acne. A comprehensive narrative review proposed that muscarinic receptors on sebaceous gland cells are the target, with downstream effects on lipogenesis and gland size (27). The clinical correlates line up: reductions in sebum casual levels, less visible pores, and improvement in the porphyrin signal on multispectral facial imaging (26,28).

In practice, microbotox can be offered to a population that historically had no useful options beyond topical retinoids, isotretinoin, or hormonal therapy. The ideal candidate has persistent oiliness despite adequate topical treatment, enlarged pores in the T-zone, and a tendency to develop comedones rather than inflammatory papules. Patients with active, severe inflammatory acne are not good candidates – needle passes through actively inflamed lesions risk seeding infection and worsening pigmentation in the short term. The treatment cycle is typically every four to six months, with the first follow-up at one month to document response using standardized photography or a multispectral imaging system. Patients should be told what the treatment will not do: it will not eliminate scarring, it will not change the underlying tendency toward acne, and it will not work as well in genuinely dry or thin skin. When expectations are properly set, satisfaction is high, and the treatment fits naturally into the same maintenance schedule patients already use for upper-face neuromodulation.

Scar Prevention and Modulation

Perioperative BoNT-A injection adjacent to an excisional wound reduces dynamic tension across the healing scar. It relaxes muscles that would otherwise distract the wound edges and may also modulate fibroblast activity and TGF-β signaling. A pooled meta-analysis of randomized trials evaluating BoNT-A for postoperative facial scar prevention found consistent improvements in scar width, Vancouver Scar Scale scores, and patient and observer assessments compared with saline controls (39). The single-dose perioperative regimen is operationally simple and uses doses comparable to standard cosmetic injections, making its incorporation into routine excisional and Mohs reconstruction practice straightforward (40). The technique seems to deliver the most benefit in the forehead, glabella, perioral area, and central chin, where high baseline muscular tension on the closed wound is common. Optimal timing is at the close of surgery or within 24–72 hours, before fibroblast proliferation peaks. Doses range from 15–30 units, distributed perilesionally within 1–2 cm of the wound margin, with care to avoid functionally critical muscles in periocular or perioral wounds. The technique is also being explored as an adjunct to corticosteroid injection in established hypertrophic scars and keloids, where the combination may outperform either modality alone.

Other Off-Label Dermatologic Uses

The list of off-label dermatologic indications continues to grow. Hidradenitis suppurativa, Raynaud phenomenon, post-herpetic neuralgia, chronic itch, hypertrophic scar and keloid management, and refractory anal fissure have all been catalogued in narrative reviews (41). Most of these fall outside the strictly aesthetic remit, but several intersect with the aesthetic practice population. Hidradenitis suppurativa of the axillary, inguinal, and submammary regions is the most obvious example: BoNT-A can complement laser hair reduction and surgical management in patients who are already visiting the same clinic for cosmetic reasons.

Combination Treatment Strategies

Modern facial rejuvenation rarely relies on a single modality. The Global Aesthetics Consensus on hyaluronic acid fillers and BoNT-A explicitly framed rejuvenation as a three-dimensional problem requiring simultaneous attention to muscle dynamics, volume, and the skin envelope. The solution is a combined neuromodulator, filler, and device protocol (42,43). The same consensus argued for a paradigm shift: neuromodulation rather than paralysis, lower upper-face dosing, more

frequent BoNT-A–filler combination treatments, and intracutaneous injection where it makes sense to limit depth of action (42).

A more focused consensus addressed the combination and sequencing of BoNT-A, hyaluronic acid filler, calcium hydroxylapatite, and microfocused ultrasound with visualization (MFU-V) across all Fitzpatrick skin types. The panel agreed on several practical points: conduct a thorough assessment and write an individualized plan; where possible, space consecutive treatments one to two weeks apart to review intermediate results; if a same-day combination is needed, perform MFU-V first, then BoNT-A and filler in either order (44). A 2024 systematic review of biostimulator combinations – poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) with energy-based devices and BoNT-A – confirmed measurable improvements in skin texture, elasticity, and contour. It also documented an adverse-event rate of 15–30%, mostly bruising, erythema, and palpable nodules, plus rare but serious events, including granulomas and vascular occlusion (45). The take-home is straightforward. Combination amplifies results. It also amplifies the consequences of poor technique, weak counseling, and absent complication-management protocols.

On the practical side, BoNT-A is usually administered first or simultaneously with fillers and biostimulators. The kinetic effect peaks at 10–14 days. Energy-based devices that cause dermal thermal injury – radiofrequency microneedling, fractional ablative lasers, MFU-V – are typically delivered before injectables to avoid disturbing freshly placed product. Patients are advised to avoid strenuous exercise, alcohol, and prone facial positioning for 24 hours after the BoNT-A injection to limit unintended migration. When microbotox is combined with hyaluronic acid filler in a single visit, the microdroplets are injected first into the dermis, followed by deeper filler placement at supraperiosteal or subdermal levels. Reversing the order risks displacing the small volumes of intradermal toxin during cannula passage.

Safety, Immunogenicity, and Resistance

BoNT-A has an excellent safety record, supported by both regulatory and post-marketing data. Common adverse events – bruising, headache, transient brow ptosis, eyelid heaviness, and asymmetric smile – are mild, self-limited, and largely technique-dependent (30,41). Microbotox shares the same profile, with one caveat: overly deep injection into muscle bellies can produce unintended weakness in areas where muscle action is needed (5).

Immunogenicity has always been the central long-term safety question. A 2024 narrative review concluded that the cumulative incidence of neutralizing-antibody (NAb) formation across BoNT-A products is low but not zero, and that it correlates with total cumulative dose, injection frequency, and product-specific protein load (46). A meta-analysis of nearly 30. 000 longitudinal subject records from 33 onabotulinumtoxinA registration trials across ten therapeutic and aesthetic indications reported NAb formation in roughly 0.5% of treated subjects. Only five subjects were classified as secondary non-responders – a remarkably low clinical-failure rate given the population size (47). The aesthetic case-report literature is humbling. Immunogenic resistance can develop even with the modest cumulative doses used in cosmetic practice, and clinicians need to stay alert to patients who report progressive loss of effect across multiple treatment cycles (48). Computational immunogenetics work using HLA-binding prediction is beginning to explain why some patients are more susceptible than others, with class II HLA polymorphisms appearing to modulate epitope presentation (49). The practical implications follow. Do not use unnecessarily short retreatment intervals – the historic 'four-week boost' should be retired. Lean toward products with lower accessory-protein load in patients heading for high cumulative doses. And have a frank conversation with anyone starting long-term maintenance about the small but real risk.

The structural characteristics of individual BoNT-A products almost certainly matter for immunogenic risk, though the data remain incomplete. IncobotulinumtoxinA is formulated without complexing proteins (the so-called naked 150-kDa neurotoxin). DAXI replaces human serum albumin with a synthetic peptide stabilizer. Both reduce the foreign-protein load per injection. Whether that translates into clinically meaningful reductions in NAb formation over decades of repeated use remains unproven. The existing comparative literature is dominated by short-term studies and indirect inferences from therapeutic neurology populations, who receive much higher cumulative doses than any aesthetic patient ever will. The defensible counseling position is honest: every currently marketed BoNT-A product carries a low but non-zero risk of secondary non-response; that risk increases with cumulative dose and frequency rather than with any single treatment; and no product can be sold to a patient as 'immunogenicity-free' on current evidence. Patients who develop apparent resistance should ideally have serum samples tested for NAb, where commercial assays are available. A switch to a different formulation with a lower complex-protein load is a reasonable next step, and if continued treatment is desired, longer treatment-free intervals give antibody titers time to wane.

One more population deserves attention. Patients who receive BoNT-A for both aesthetic and therapeutic indications – chronic migraine, cervical dystonia, hyperhidrosis, overactive bladder – accumulate cumulative doses well above those of purely aesthetic patients. These variants are considered to be associated with the highest immunogenic risk. Dual-indication patients should be managed with a unified treatment plan that accounts for total annual exposure and avoids redundant or overlapping injections. The aesthetic injector who cares for such a patient should be in contact with the prescribing neurologist or other treating physician regarding dosing intervals and product selection.

Complications and Their Management

Upper-Face Complications

The upper face accounts for the largest share of clinically significant adverse events, partly because injection sites lie near functionally critical periocular structures and partly because these treatments are so frequent. Brow ptosis results from inadvertent diffusion of glabellar or frontalis injections into the frontalis below the supraorbital rim, or from selective weakening of the medial frontalis without corresponding weakening of the lateral fibers. Onset is delayed (3–10 days post-injection), and the condition resolves spontaneously over six to eight weeks. Symptomatic relief during recovery can be achieved with apraclonidine 0.5 % drops, which stimulate the Müller's muscle and elevate the upper eyelid by 1–2 mm. Eyelid ptosis is the more disabling problem. It results from migration of glabellar injection through the orbital septum to the levator palpebrae superioris. Prevention is built into proper technique. Glabellar injections are placed at least 1 cm above the supraorbital rim and angled slightly superiorly and laterally toward the orbital margin (43).

Brow asymmetry, including the Mephisto sign mentioned earlier, results from uneven dose distribution across the frontalis or from differential effects on the lateral and medial brow elevators and depressors. Mild asymmetry can usually be corrected at a two-week follow-up by touching up the underdosed side. This approach is more effective than trying to correct the overdosed side, which relies on diffusion or natural recovery. Patients should know up front that minor asymmetric responses are common and that the two-week fine-tuning is part of the treatment, not evidence of a “botched” outcome.

Diplopia and other ocular adverse events are exceptionally rare in aesthetic practice, but they have been reported after lateral canthal injection that diffused to the lateral rectus and after a misplaced glabellar injection that reached the inferior oblique. Any patient reporting diplopia or persistent visual disturbances following upper-face injection requires urgent ophthalmologic referral. Prophylactic measures are simple: conservative dosing in the lateral canthal region and strict adherence to the rule of injecting outside the orbital rim.

Lower-Face Complications

The lower face has a distinct complication profile, predominantly characterized by smile asymmetry, oral incompetence, and disturbances in articulation. Asymmetric smile after masseter injection results from anterior diffusion into the risorius or zygomaticus minor. Staying within the safe-zone triangle prevents it. Pinching the masseter belly during injection confirms muscle depth and minimizes anterior spread by tenting the muscle away from neighboring superficial musculature.

Oral incompetence following perioral or depressor anguli oris (DAO) injection presents as drooling, difficulty drinking through a straw, or impaired plosive consonants. The risk increases steeply with dose escalation. Staying within the conservative ranges in Section 4 and Table 2 substantially reduces the incidence. Some patients are particularly vulnerable: those with pre-existing partial facial nerve weakness, post-surgical scarring of the perioral region, or compromised lip tone (after extensive prior filler placement, for example). They should be counseled carefully or excluded outright. Recovery is typically spontaneous and complete by four to six weeks.

Microbotox-Specific Complications

The intradermal microdroplet technique has its own pattern of complications. Bruising is the most common, more frequent than with the traditional intramuscular technique, simply because of the high number of injection points and the proximity of fine-needle passes to superficial dermal vessels. Patients should stop elective antiplatelet supplements (omega-3 fish oils, vitamin E, ginkgo, garlic, etc.) for at least three days before treatment, avoid alcohol for 24 hours pre- and post-procedure, and be informed that mild ecchymosis for one to seven days is expected. Erythema and edema usually resolve within hours but can persist for one to two days in reactive skin or alongside combined treatments such as fractional laser. Asymmetric weakness of fine facial expression – affecting the lower lip, the lateral lip, or one side of the smile – occurs when a

microdroplet is deposited too deeply and reaches the muscle below. Strict attention to depth (0.5–1.5 mm within the dermis) and avoidance of excessive pressure during injection (which pushes the toxin posteriorly) substantially reduce the risk.

Vascular Events and Anaphylaxis

Vascular embolic events from BoNT-A alone are not biologically plausible. The injected volumes are small, and the toxin itself does not cause vessel occlusion. Vascular events do occur with combination treatments, in which filler is injected during the same session, but the filler, not the toxin, is the offending agent. Distinguishing immediate post-injection erythema from early vascular compromise is critical. Erythema from needle trauma blanches with pressure and resolves within hours. Vascular embolic erythema is dusky, follows a vascular distribution, and is accompanied by pain that is disproportionate to the injection. The standard response to a suspected vascular event is immediate cessation of injection, hyaluronidase flooding (300–1500 IU, depending on filler volume), warm compresses, and aspirin if there is no bleeding contraindication. True anaphylactic reaction to BoNT-A is exceptionally rare. The few case reports attribute it to human serum albumin or other excipients rather than the neurotoxin itself (42).

Emerging Trends and Future Directions

Several lines of research will likely shape the next decade of aesthetic neuromodulation. Liquid-stabilized formulations and ready-to-use preparations eliminate the reconstitution step, thereby reducing one of the most common sources of inter-clinic outcome variability. Topical and microneedle-delivered BoNT-A platforms are being investigated as needle-free or minimally invasive alternatives, with potential application to large surface areas where conventional intradermal microdroplet injection is impractical (27). Long-acting formulations like DAXI may continue to extend treatment intervals. The trade-off between duration and immunogenicity warrants careful longitudinal study – prolonged tissue exposure to a large protein antigen may, in principle, increase the risk of sustained antibody-mediated neutralization (7,9). Non-toxin neuromodulator candidates targeting downstream SNARE biology, peripheral neurotransmitter receptors, or sebocyte cholinergic signaling are in early clinical development. If effective, they may offer alternatives for patients who develop resistance or are otherwise unsuitable for botulinum toxin therapy.

Practice is also changing in less obvious ways. Artificial intelligence–based facial assessment, three-dimensional imaging, and predictive modeling of post-injection outcomes are beginning to influence treatment planning. Standardized photographic protocols, validated patient-reported outcome instruments such as FACE-Q, and shared electronic injection-mapping records are becoming the norm in advanced practices and regulatory submissions. The methodological bar has risen for both clinical care and clinical research. Patient demographics are shifting as well. The “preventive Botox” cohort of patients in their twenties and early thirties is the fastest-growing segment in many large registries. Male aesthetic patients, who require different dosing patterns to preserve characteristic brow position and overall facial dynamics, are reshaping what a typical injection map looks like.

Finally, the regulatory and ethical landscape surrounding off-label aesthetic BoNT-A is slowly catching up. Many of the techniques covered in this review—microbotox, masseter contouring, the Nefertiti lift, gummy-smile correction, and intradermal injection for rosacea or scar modulation—remain off-label in most jurisdictions, even though the supporting literature is robust and clinical adoption is widespread. The work ahead includes harmonizing regulatory frameworks, establishing minimum training standards for advanced injection techniques, and ensuring that informed consent for off-label use is genuinely informed rather than nominal. None of that will happen quickly. But the field is, more or less, ready for it.

Conclusions

BoNT-A is no longer the single-indication wrinkle relaxant it was twenty years ago. It is a platform for whole-face rejuvenation, contour refinement, skin-quality improvement, and an expanding range of dermatologic indications. The peptide-stabilized DAXI, broader use of prabotulinumtoxinA and letibotulinumtoxinA, routine adoption of the intradermal microdroplet technique, sophisticated lower-face and neck protocols, and evidence-based combination strategies together form a recognizable modern field. At the same time, the rapid expansion of off-label use, persistent variability in dosing protocols across products, and incomplete long-term immunogenicity data for newer formulations argue for more rigorous comparative trials, harmonized practice guidelines, and continued discipline in patient selection and complication prevention. In the end, the injector matters more than the brand. Deep anatomical knowledge, current pharmacologic literacy, and disciplined technique still produce safe, natural-looking results.

Two final practical points are worth stating directly. The first concerns honesty with patients. Aesthetic medicine sells outcomes that are visible and personal, which creates pressure to overpromise. The literature reviewed here supports a different posture. Microbotox does not replace a facelift. Masseter BoNT-A does not, on its own, produce a chiseled jawline in every patient. Long-acting formulations do not eliminate concerns regarding immunogenicity. A more useful conversation begins by acknowledging what the data show, including their limitations. The second point concerns the injector's learning curve. Cadaveric anatomical study, observation of experienced colleagues, and a detailed personal log of doses, injection maps, and follow-up photographs matter more in this field than any single course or product training. There are no shortcuts. The patient in front of you will appreciate the rigor of that long process.

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