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Role of Botulinum Toxin in Sebum Regulation and Acne Vulgaris: A Mini Review

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Abstract:

Background: Botulinum toxin is a potent neurotoxin produced by Clostridium botulinum and has been used clinically since the late 1970s. Among its different serotypes, botulinum toxin type A is the most widely used in medical and aesthetic practice because of its ability to inhibit acetylcholine release at neuromuscular junctions and autonomic nerve terminals. In dermatology, botulinum toxin has established and emerging roles in both cosmetic and non-cosmetic indications, including hyperhidrosis, facial wrinkles, facial contouring, rosacea, wound healing, scar prevention, keloids, hypertrophic scars, and several inflammatory skin disorders. Recently, intradermal botulinum toxin A has gained attention as a potential treatment for oily skin, enlarged pores, seborrhea, and acne vulgaris. Its proposed therapeutic effect in acne is mainly related to reduction of sebum secretion through inhibition of cholinergic stimulation of sebaceous glands and paralysis of arrector pili muscles, thereby decreasing sebum output on the skin surface. Although current evidence suggests promising benefits, further well-designed studies are still required to standardize dosing, injection techniques, efficacy, and safety in dermatological practice.

Keywords: Botulinum toxin; Botulinum toxin A; Dermatology; Acne vulgaris; Sebum reduction; Oily skin; Hyperhidrosis; Cosmetic dermatology.

Introduction:

Botulinum toxin is a powerful neurotoxin generated by Clostridium botulinum, a bacterium known for its spore-forming, gram-positive, and anaerobic properties. This neurotoxin has been employed in clinical practice since the late 1970s. Clostridium botulinum produces seven serotypes of botulinum neurotoxins, labeled A through G, with four types being utilized for practical applications. Of these, serotype A comprises three types, while serotype B accounts for one **(1).**

In the 1970s, it was discovered that Botulinum neurotoxin BoNT-A had therapeutic potential, making it the most widely used BoNT in clinical applications **(2).** Additionally, BoNT-A was approved by the FDA in 1989 for the treatment of blepharospasm and strabismus. Further research has led to the development of new formulations and expanded the range of indications **(3).** In 2002, the FDA approved the use of BoNT-A for cosmetic purposes **(4).** As a result, BoNT-A has become widely used by neurologists and cosmetic practitioners **(3).**

Several novel BoNT formulations, including synthetic and genetically engineered variants, have been developed in recent years. These formulations exhibit distinct pharmacological properties. Currently, over six BoNT products are approved for clinical use, with additional candidates under development. Understanding the specific characteristics of each formulation is crucial for prescribers, particularly when considering their interchangeability **(3).**

Initial 19th-century observations linked a toxin from spoiled food to botulism symptoms, leading to the hypothesis that low doses could treat hyperactive nerve disorders. By the 20th century, various BoNT serotypes were identified, and BoNT/A was shown to inhibit acetylcholine release at neuromuscular junctions **(5).**

This discovery paved the way for its clinical application in the 1970s, beginning with the treatment of strabismus. Botulinum toxin is widely used for autonomic dysfunctions, spasticity, hyperkinetic disorders, and cosmetic procedures. BoNT/A is approved for conditions including upper limb spasticity, blepharospasm, hemifacial spasm, cervical dystonia, primary hyperhidrosis, and neurogenic detrusor overactivity **(6).**

Mechanism of botulinum neurotoxins:

BoNT/A exerts its effect through five key steps.

1-Neurospecific Binding

2-Entry into Nerve Terminals

3-Synaptic Vesicle Membrane Translocation

4-Reduction of the Disulphide Interchain Bond

5-SNARE Protein Cleavage **(Figure 1) (7).**

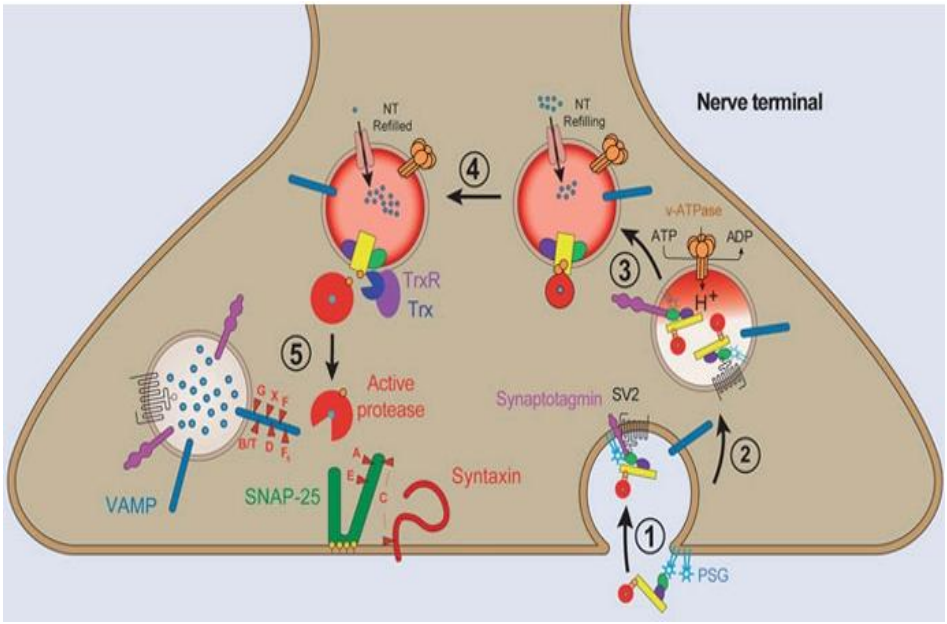

Figure 1: Mechanism of botulinum neurotoxins entry and paralysis of nerve terminals **(8).**

The entry of botulinum neurotoxins (BoNTs) into nerve terminals and the subsequent induction of paralysis is a multistep process. Initially, the C-terminal domain of the heavy chain (HC-C) binds to a polysialoganglioside (PSG) receptor on the presynaptic membrane, followed by interaction with a protein receptor within the lumen of synaptic vesicles. The currently identified protein receptors include synaptotagmin, which serves as the receptor for BoNT serotypes B1, DC, and G, and glycosylated synaptic vesicle glycoprotein 2 (SV2), which acts as the receptor for BoNT serotypes A1 and E1. Following receptor binding, the toxin is internalized into synaptic vesicles. Subsequently, vacuolar-type ATPase (v-ATPase) acidifies the vesicular lumen, generating a proton gradient that drives neurotransmitter accumulation via vesicular neurotransmitter transporters. This acidification also induces conformational changes that allow the light chain (L chain) of BoNT to translocate across the vesicular membrane into the cytosol, a process assisted by the N-terminal domain of the heavy chain (HN domain), although the exact mechanism remains incompletely understood **(8).**

Once in the cytosol, the L chain is released from the HN domain by the thioredoxin reductase–thioredoxin (TrxR–Trx) system, which reduces the interchain disulfide bond. The L chain then exhibits its zinc-dependent endopeptidase activity, targeting critical components of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex. Specifically, BoNT serotypes B, D, F, G, and X cleave vesicle-associated membrane protein (VAMP); BoNT serotypes A and E cleave synaptosomal-associated protein of 25 kDa (SNAP-

25); whereas BoNT serotype C cleaves both SNAP-25 and syntaxin. Each of these proteolytic events is independently sufficient to block neurotransmitter release for a prolonged duration, resulting in neuroparalysis. These observations highlight VAMP, SNAP-25, and syntaxin as essential core elements of the nanomachine that mediates neurotransmitter release at the synaptic cleft **(8).**

The prolonged effect of BoNT/A after a single administration is primarily due to its structural components that ensure high-affinity binding to neuronal targets and precise intracellular activity. BoNT/A cleaves synaptosomal-associated protein 25 (SNAP-25), a key component of the SNARE complex involved in neurotransmitter release. Its sustained action is largely attributed to the remarkable stability of the BoNT/A protease, which evades cellular degradation and remains active in the cytoplasm for an extended duration **(5).**

Types of Botulinum toxin:

There are several types of botulinum toxin, Botulinum neurotoxin type A includes different formulations such as Abobotulinum toxinA (Dysport), Incobotulinum toxinA (Xeomin), and Onabotulinum toxinA (Botox). Another serotype, Botulinum neurotoxin type B, is available as Rimabotulinum toxinB (Myobloc) **(3).**

Table(1): Molecular characteristics of conventional botulinum toxin preparations. (3).

ProprietaryName	Serotye	Strain	Complex Size	Excipient	Stabilisation and Solubilisation	Unit/Vial	Neurotoxin Protein (ng/vial)
Botox (onabotulinumtoxinA)	A	Hall	900kD	HSA(500 g) Sodiumchloride	Vacuumdrying and normal saline	50,100, 200	5
Xeomin (Incobotulinumtoxin A	A	Hall	150kD	HSA(1 g) Sucrose	Lyophilisation and normal saline	100,200	0.6
Dysport (Abobotulinumtoxin A)	A	Hall	500kD	HSA(125 g) Lactose	Lyophilisation and normal saline	300,500	435
Myobloc/Neurobloc (Rimabotulinumtoxin B)	B	Bean	700kD	HSA(500 g/mL) Sodiumsuccinate Sodiumchloride solution	solution	2000,5000, 10,000	~25,50, 100

Storage and Reconstitution

Botulinum toxin A comes as a part of lyophilized structure while Botulinum toxin B comes prediluted and prepared for use. They ought to be reconstituted in 0.9 % sterile saline, delicately brought into the vial maintaining a strategic distance from air pocket arrangement **(9).**

Studies conducted with onabotulinum toxin and abobotulinum toxin have shown that botulinum toxin are effective for long time after reconstitution from two to six weeks**.**The dose conversion ratio is estimated to range from 1:2 to 1:4 **(10).**

Microbotox, or mesobotox, involves injecting multiple small droplets of diluted BoNT-A into the dermis or the area between the dermis and superficial facial muscles, glands, and skin structures. This technique, known

as microbotulinum toxin A (micro BoNT-A), aims to preserve facial mobility and natural beauty while targeting specific facial areas with minimal invasiveness **(11).**

Meso-Botox is typically prepared by diluting onabotulinum toxin A (ONA) in normal saline. Common protocols include a 1:5 dilution (100 U in 5 mL) or a 1:10 dilution (100 U in 10 mL), with dosing adjusted according to the treatment area. Alternatively, a standard dilution of ONA (2.5 mL saline to 100 U) may be further diluted, according to the area being addressed, for example, 24 U (0.6 mL in a 40 U insulin syringe, topped up with saline) providing 24 U in 1 mL solution while treating the forehead, similarly 8–12 U for the under-eye area and 24 U for the neck and jawline **(12).**

Medical application of dermatology:

Non cosmetic indications

In dermatology, the only FDA-approved medical use of ONA is for axillary hyperhidrosis. Off-label indications include alopecia, bullous skin disorders, palmar and plantar hyperhidrosis, hypertrophic and keloidal scarring, and other conditions such as Raynaud's phenomenon, hidradenitis suppurativa, and psoriasis **(13).**

Hyperhidrosis

Botulinum neurotoxin inhibits acetylcholine-mediated secretion from eccrine sweat glands. ONA is FDA-approved for primary axillary hyperhidrosis, but its use has expanded to the palms, soles, and other areas. Standard protocols involve 50–100 U per axilla injected intradermally in a grid pattern, producing results within a week that last 3–10 months. Treatment of the palms and soles requires higher doses (75–100 U per hand, 100–200 U per foot) with effects lasting 3–6 months, but may cause transient weakness or gait difficulties. Pain during injections can be reduced using topical anesthetics, cryoanalgesia, microneedles, jet injectors, or nerve blocks. BoNT has also been effective for Frey's syndrome, sialorrhoea, chromhidrosis, bromhidrosis, and even dyshidrotic eczema **(14).**

Alopecia

Botulinum toxin type A has been trialed in androgenetic alopecia, cephalalgic alopecia, alopecia areata, and radiation-induced alopecia. The proposed mechanism involves reduced microvascular pressure through muscle relaxation, enhancing oxygen delivery to hair follicles. Treatment protocols vary from 30–150 U across the frontal, temporal, periauricular, and occipital regions over 1–12 sessions. Most studies report improved hair growth or density with high patient satisfaction, though randomized controlled trials are still needed. Conversely, repeated forehead BoNT-A injections have been associated with frontal alopecia **(15).**

Bullous Skin Diseases

Botulinum toxin type A has shown benefit in Hailey-Hailey disease, linear IgA bullous dermatosis, and localized epidermolysis bullosa simplex. In Hailey-Hailey, injections of 25–200 U every 3–6 months, sometimes combined with laser therapy or tacrolimus, produced clinical improvement lasting up to 12 months. Case reports describe treatment with 50 U/axilla for linear IgA dermatosis and 100 U for localized epidermolysis bullosa simplex, with symptomatic relief **(16).**

Raynaud's Phenomenon

Botulinum toxin type A has been used successfully for primary and secondary Raynaud's phenomenon unresponsive to conventional therapies. Injection of 50–100 U into the digits improves pain, digital ulcers, and vasospasm, with significant increases in digital pulp temperature compared to saline controls. No standardized protocol exists, but injections at the wrist, digits, or distal metacarpus yield comparable outcomes **(17).**

Wound Healing and Scar Prevention

Botulinum toxin type A has been demonstrated to play a significant role in wound healing and scar prevention by modulating both mechanical and cellular factors involved in scar formation. BoNT-A induces temporary paralysis of the muscles surrounding a wound, thereby reducing tension vectors that contribute to scar widening and hypertrophy. At the cellular level, BoNT-A inhibits fibroblast proliferation and prevents fibroblast-to-myofibroblast differentiation, leading to decreased secretion of transforming growth factor beta 1 (TGF-β1)

and connective tissue growth factor, ultimately reducing excessive collagen deposition in the dermal layer. Clinical studies have shown that scars treated with BoNT-A exhibit improved aesthetic outcomes, including better pliability, reduced collagen density, and closer resemblance to normal skin, highlighting its potential application in preventing hypertrophic and cosmetically undesirable scars after trauma, burns, or surgical procedures **(18).**

Keloids and Hypertrophic Scars

By inducing temporary chemoimmobilisation, BoNT-A reduces mechanical stress across healing wounds, which is believed to attenuate the inflammatory and fibrotic processes underlying scar hypertrophy. Clinical studies, including randomized controlled trials, have demonstrated that intralesional BoNT-A can significantly decrease keloid volume, height, and redness, with additional benefits in reducing associated pain and pruritus. Furthermore, BoNT-A used as a postsurgical adjunct following keloid excision has shown improved scar pliability, aesthetic outcomes, and patient satisfaction, with a lower incidence of side effects compared to corticosteroid therapy **(19).**

Rosacea

Botulinum toxin has emerged as a promising therapeutic option for rosacea, particularly for erythematotelangiectatic and refractory forms. Its mechanism involves the inhibition of acetylcholine and vasoactive neuropeptides, such as VIP, reducing vasodilation and facial redness. Additionally, BoNT-A directly suppresses mast cell degranulation, therapy attenuating inflammation and erythema. Clinical studies have demonstrated that intradermal injections of BoNT-A can significantly decrease erythema, telangiectasia, and flushing, improve skin elasticity and hydration, and enhance patient satisfaction, with a favorable safety profile when administered in controlled doses **(20).**

Other Dermatologic Diseases

Botulinum toxin type A has been reported effective in hidradenitis suppurativa (40–250 U) with remission lasting 6 months to 3 years, likely due to reduced sweating and bacterial growth. Additional off-label uses include aquagenic keratoderma, congenital eccrine nevus, Darier disease, psoriasis, notalgia paresthetica, pachyonychia congenita, and post-herpetic neuralgia, with varying levels of clinical success **(13).**

Cosmetic indications

Beyond its established FDA-approved indications, botulinum toxin is increasingly utilized off-label for various aesthetic purposes, including treatment of the upper and midface (e.g., eyebrow lift, bunny lines, lowered nasal tip), lower face (e.g., gummy smile, perioral rhytids, drooping oral commissures, dimpled chin, platysmal bands), oily skin , pore size reduction, rosacea, and contouring of the face **(21).**

Wrinkles

Botulinum toxin type A is widely used for the treatment of facial wrinkles. Its primary mechanism involves the temporary inhibition of acetylcholine release at the neuromuscular junction, which prevents muscle contraction and induces relaxation of the targeted facial muscles. This muscle paralysis smooths dynamic wrinkles such as glabellar lines, crow's feet, and forehead creases that appear during facial expression. The clinical effects usually begin within 24 to 72 hours, peak after one to four weeks, and last for about three months **(22).**

Vertical Perioral Rhytids

Perioral rhytides result from the sphincteric action of the orbicularis oris, a muscle encircling the lips and inserting into the perioral skin. Treatment typically involves low-dose ONA (2–3 U) injected along the vermilion border while the patient contracts the lips, which softens vertical wrinkles. Although complications such as flattening of the vermilion border, lip asymmetry, or altered function may occur, these effects are dose-dependent **(23)**.

EyebrowLift

Onabotulinum toxinA is a cornerstone in minimally invasive facial rejuvenation, particularly for eyebrow reshaping and elevation. By selectively weakening the brow depressor complex (procerus, corrugator supercilii, depressor supercilii, orbicularis oculi) and modulating frontalis activity, the balance between opposing muscles is restored, leading to a smoother forehead and a natural brow lift. Standardized injection protocols, typically 4 U into each glabellar depressor and 2 U at defined points of the frontalis, have been shown to achieve predictable cosmetic outcomes while minimizing complications such as brow or lid ptosis, asymmetry, and the mephisto sign **(24)**

Bunny Lines

Nasalis fanning rhytides, commonly referred to as "bunny lines," result from contraction of the transverse nasalis and medial orbicularis muscles, producing horizontal wrinkles across the nasal bridge. Management typically involves injecting 3–5U of ONA, bilaterally into the upper nasalis or lateral nasal wall, with higher placement on the dorsum to prevent diffusion into the levator labii complex and subsequent lip ptosis **(25).**

Lowered Nasal Tip

Nasal tip ptosis frequently associated with hyperactivity of the depressor septi nasi muscle and age-related changes can be effectively corrected with targeted botulinum toxin injections into the columella. Standard dosing involves 2–5U of ONA at the depressor septi insertion, occasionally supplemented with small aliquots to the levator labii superioris alaeque nasi **(21).**

Gummy Smile

Onabotulinum toxinA has emerged as a minimally invasive option for correcting gummy smile by targeting hyperactive elevator muscles of the upper lip, thereby reducing excessive gingival display. Clinical studies included in systematic reviews demonstrated that doses ranging from 2.5 to 5 U per site can achieve a reduction of 3–5 mm in gingival exposure, with optimal results observed at two weeks and lasting approximately three to four months. This approach provides safe, reversible, and aesthetically pleasing outcomes, particularly in patients whose gummy smile is primarily muscle-related **(26).**

Drooping Oral Commissures

Drooping oral commissures result from hyperactivity of the depressor anguli oris muscle, which pulls the mouth corners downward and produces a sad facial expression. Targeted ONA injections (4–10 U) placed subdermally about 1 cm lateral and inferior to the oral commissure can effectively elevate the corners. Anatomical variations, such as the lower position of the modiolus in Asian patients, may influence injection sites, while inaccurate placement risks functional complications including asymmetry or impaired lower lip movement **(27).**

Dimpled Chin

The cobblestone or dimpled chin results from hyperactivity of the mentalis muscle, which inserts fibers into the dermis and elevates the chin and lower lip. BoNT injections target the mentalis to relax its contraction, reducing the cobblestone appearance, softening the mental crease, and refining the chin contour. Optimal injection requires understanding the mentalis anatomy, with deep (3 U) and superficial (1 U) injections administered 0.5 cm lateral to the pogonion. Careful anatomical targeting minimizes complications such as lower lip ptosis or asymmetric expressions. This approach allows effective, safe, and precise management of chin dimpling in aesthetic practice **(28).**

Platysmal Bands

Platysma bands are vertical neck cords caused by hyperactive platysma muscle, often associated with skin laxity and lipodystrophy. Botulinum toxin provides a minimally invasive alternative to surgery, with 2–6 intramuscular injections per band using up to 20 IU incobotulinum toxinA or 5 IU abobotulinum toxinA. Complications are minor, with ecchymosis/hematoma reported in 15% of patients **(29).**

Contouring of the face

Masseter muscle hypertrophy is a common cause of a broad or square lower face, often leading to cosmetic concerns. Traditionally managed with surgical approaches, botulinum toxin type A (BTA) injections have emerged as a minimally invasive and effective alternative for lower face contouring. By inducing chemodenervation and temporary atrophy of the masseter muscle, BTA reduces muscle bulk and reshapes the jawline, with maximum effect typically observed after 3 months and lasting 6–12 months. Although optimal dosage and injection technique vary, evidence consistently supports BTA as a safe and reliable method for facial contouring, with side effects generally mild and transient **(30).**

The role of botulinum toxin in acne vulgaris

Oily skin

Botulinum toxin has shown potential as a treatment for oily skin, first reported in 2002 as a side effect of forehead injections **(31).** Subsequent studies demonstrated reduced sebum production and smaller pore size after intradermal injections **(32).** A randomized, double-blind trial later confirmed that intramuscular injections decreased sebum at treated sites but increased production in surrounding areas **(33)**.Current evidence suggests intradermal administration may be more effective, although larger studies are required to validate this approach **(34).**

The mechanism is not yet fully understood. It is proposed that BoNT-A modulates sebaceous gland activity via effects on erector pili muscles and blockade of local acetylcholine receptors, thereby influencing sebocyte differentiation and sebum output **(32, 34).**

Pore Size and Sebum Reduction

Enlarged facial pores and excessive sebum production remain a therapeutic challenge with considerable psychosocial impact. Intradermal BoNT-A has been explored as a potential intervention, with initial studies reporting improvements in sebum production and pore size in 85% of 20 patients. Objective measurements using a sebometer demonstrated significant sebum reduction lasting up to three months, with 91% patient satisfaction. Both 10 U and 20 U doses were shown to significantly decrease sebum output, although the effects returned to baseline after 16 weeks. However, a randomized split-face study found no significant reduction in pore size or sebum production. Collectively, these findings indicate that intradermal BoNT-A can modulate sebaceous gland activity and potentially improve pore appearance, though the evidence is limited and results remain inconsistent (**32, 33).**

Finally, Intradermal BoNT-A injection may represent an innovative promising treatment for oily skin and other relevant dermatological problems, such as enlarged pores, acne, and seborrheic dermatitis **(35).** The pathophysiology of acne vulgaris involves multiple factors, with the primary contributors being enhanced sebum production, the colonization of hair follicles by Propionibacterium acnes, and abnormal keratin accumulation **(36).**

Botulinum toxin type A has demonstrated the ability to decrease sebum secretion from sebaceous glands, with proposed mechanisms including the inhibition of acetylcholine release in sebocytes and the induction of flaccid paralysis in the arrector pili smooth muscle of hair follicle units. Since contraction of the arrector pili muscle is necessary for sebum secretion, its paralysis leads to a reduction in sebum production on the skin's surface. There is no evidence supporting an antibacterial effect of BoNT-A, which suggests that the reduction in sebum production is likely the main mechanism through which BoNT-A helps alleviate acne vulgaris **(37).**

Side Effects of BoNT/A

Common side effects of BoNT/A injections include localized bleeding, swelling, erythema, and pain at the injection site. These can often be minimized by using fine-gauge needles and diluting the toxin with saline. Post-injection headaches may also occur but typically resolve within 2–4 weeks and can be managed with systemic analgesics. Other reported adverse effects include malaise, nausea, influenza-like symptoms, and transient ptosis, particularly when treating the glabellar region. Ptosis results from local diffusion of the toxin and can persist for several weeks, but may be alleviated with alpha-adrenergic agonist eye drops **(38).**

Ectropion may occur if BoNT/A spreads to the lower eyelid during periorbital treatments. Additionally, unintended diffusion of the toxin in the treatment of crow's feet or bunny lines can lead to strabismus.Despite these complications, most side effects are temporary and resolve as the neuromuscular blockade diminishes **(38).**

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