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ORIGINAL CONTRIBUTION

Current use of botulinum neurotoxin in esthetic practice—Clinical guide and review

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Abstract

Background: Botulinum neurotoxin is one of the most versatile and widely used medical products in the world.

Aims: The review's focus is the plastic and dermatologic uses of botulinum neurotoxin currently supported by published data.

Methods: Relevant clinical articles regarding botulinum neurotoxin use in plastic surgery, dermatology, and general esthetic literature were searched and reviewed.

Results: The search yielded 258 studies. Two hundred articles were excluded following title and abstract review. Twenty-one studies were excluded following full-text screening. A total of 37 studies remained and were discussed in this review.

Conclusions: Botulinum neurotoxin is widely used for numerous off-label indications from head to toe. Some uses are well documented, and their safety has been demonstrated in controlled trials, yet most remain poorly researched.

KEYWORDS
aging, Botox, botulinum neurotoxin, Dysport, injectables

1 | INTRODUCTION

Botulinum neurotoxin (BTX) is derived from the gram-positive, rod-shaped, spore-forming bacterium *Clostridium botulinum*. Seven different toxins (A to G) originate from different strains of *C. botulinum*. Types A, B, E, and F are most commonly associated with human disease.[1] Types A and B are available for commercial use, and since type A is the most potent form, it the most frequently used clinically.[2]

The first published use of the toxin clinically was made in 1980 by Alan B. Scott, an ophthalmologist using botulinum toxin to treat strabismus. Scott used the type A formulation to weaken the muscle responsible for the strabismus.[3] He called the drug Oculinum (now known as BOTOX®) and later sold the formulation to Allergan. In 1992, Jean and Alastair Carruthers published their clinical trial of botulinum neurotoxin's first cosmetic use, showing the reduction in the glabellar lines.[4] The Food and Drug Administration (FDA) officially approved Allergan's BOTOX® (Allergan, Inc.) in 2002 to treat glabellar furrows after a study of 264 patients ushered in the cosmetic trend of botulinum neurotoxin use.[5]

The BTX mechanism of action involves blocking the neurotransmitter acetylcholine (ACh) release into the neuromuscular junction by interfering with the synaptic neural associated protein (SNAP-25).[6] Currently, many formulations of the neurotoxin are available in the United States and Europe. Most use the BTX type A formulation but differ in production.[6] This review describes the current trends of BTX use by anatomical region.

2 | MATERIALS AND METHODS

Two independent reviewers conducted an NIH National Center for Biotechnology Information (NCBI) PubMed search. Clinical articles about the use of BTX in plastic surgery and dermatology and general esthetics were identified. Message-Subject-Headings (MeSH) were applied: (Botulinum neurotoxin OR Botulinum neurotoxin treatment

OR Botulinum) AND (plastic OR dermatology OR aesthetic) AND (prevention OR minimizing OR early intervention OR treatment outcome OR rejuvenation). Human studies published in English were included.

3 | RESULTS

Two hundred twenty-four studies were initially identified and 34 additional were added from references. We excluded two hundred articles due to title and abstract. Twenty-one studies were cut following text review. Finally, 37 studies remained. Applications of BTX were organized and discussed according to location of administration, such as the hair, face, head, perioral area, chin, neck, axilla, palms, soles, breasts, and calves. Administration of BTX at each location tended to address different medical and esthetic indications.

3.1 | Hair

Many underlying disorders can manifest as alopecia. BTX has been used off-label to treat androgenetic alopecia, caused by the hair follicles' sensitivity to dihydrotestosterone. The suggested mechanism of action of the BTX in alopecia is loosening the scalp musculature and reducing perforating vessels' pressure to increase blood flow to the hair follicles.[7]

Prior studies have explored and reviewed BTX for alopecia and determined that there was a beneficial effect for alopecia, improving hair growth and hair quality[7,8]; however, more robust randomized controlled trials need to be performed to solidify the utility of BTX for alopecia. As of now, it is recommended to administer injections throughout the scalp musculature. The suggested dose involves 5 units (U) for each injection of BOTOX® regardless of the area of alopecia every 4–6 months.[8]

3.2 | Face

Botulinum neurotoxin is injected into the facial expression muscles responsible for the rhytide appearance (Figures 1 and 2) in the glabella, forehead, and lateral canthus. Each company's formulation has its reconstitution, dilution, and injection dosing to achieve the muscles' temporary paralysis to prevent rhytide formation and exacerbation. The suggested dose was described by Rohrich and Fagien using 2.5–4 U per injection site to reduce muscular tone for 3–6 months (Video S1).[2,9]

3.3 | Head

Migraine headaches may cause significant disability and an economic burden. Population-based surveillance studies during 2014 and 2015 demonstrated a prevalence of 20.7% in females and 9.7% in males.[10] By the ICDH-3 classification, chronic migraine headaches occur 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.[11] In 2010, the double-blind controlled phases of the PREEMPT 1/2 clinical program exhibited a significant reduction in chronic migraines using BTX treatment versus placebo. Prophylactic treatment for chronic migraines using BTX injections was approved by the FDA in 2010.[12,13] Also, a recent meta-analysis of 17 articles showed a

FIGURE 1 Simulated injection into the frontalis muscle as shown in body-painting scheme

FIGURE 2 Patient being marked for frontal and glabella injections of botulinum toxin

FIGURE 3 Injection into the medial lower eyelid portion of the orbicularis muscle, near the punctum

reduction in episodic migraines headaches with BTX administration.[14] It is suggested that the mechanism of action involves muscle tone reduction and inhibition of peripheral sensory signals.[14,15] Injection sites include the bridge of the nose, the forehead, the temples, the back of the head, and the neck. The suggested dose involves 5 U each injection of BOTOX® every 6 months.

3.4 | Eyes

Treatment of keratoconjunctivitis sicca, or dry eyes, has been explored using BTX off-label. Upon orbicularis muscle contraction (blinking), the nasolacrimal duct system's canaliculi shorten, assisting in the drainage of tears from the eye.[16] BTX injection lowers the blink output 3 weeks after treatment, reducing the tear drainage from the eye, and maintaining a moist eye.[17] Injection into the medial lower eyelid near the punctum (Figure 3 and Video S1) might help patients suffering from dry eyes.

However, it should be mentioned that botulinum toxin injection in the eye's proximity (after treating lateral canthal lines or crow's feet) has been associated with keratoconjunctivitis sicca syndrome. This phenomenon is speculated to be due to toxin infiltration into the lacrimal gland that interferes with the autonomic cholinergic transmission and decreases lacrimation.[18] The suggested dose for this application was exemplified using 40 U of Dysport™ (abobotulinumtoxinA, Ipsen Biopharm) every 3–6 months.

3.5 | Midface

Rosacea is erythema over the central face persisting for longer than 3 months, often can be accompanied by flushing, papules, pustules,

and telangiectasia.[18] Rosacea has many triggers such as weather, stress, physical activity, food, and drinks and can cause much distress to the patient. The pathophysiology of rosacea is unclear.[19] It is speculated that chemical denervation of the acetylcholine signaling pathways by BTX may play a part in effectively causing symptomatic relief to patients with severe facial flushing.[20] Intradermal injections are made to the affected area for this off-label indication (Figure 4). The improvement in symptoms may be seen at about 3 weeks after the first treatment and may last up to 6 months. The suggested dose ranges from 8 to 12 units BOTOX® per affected cheek area to a total dose of 50 units in two different treatments depending on the area affected.[19–24] Improvement of symptoms has lasted up to 6 months, yet further data are needed to elucidate any concrete conclusions.

3.6 | The lower third of the face

Muscle hypertrophy usually appears between the ages of 20 and 40 and can be unilateral or bilateral.[25] The condition is of an unknown etiology and can be associated with bruxism. Masseteric hypertrophy may enlarge the mandibular angle area, cause pain, and limit the mouth's opening.[26] Off-label intramuscular injections BTX to the masseter muscle were described to alleviate these issues with avoidance of the parotid gland, injecting mid muscle (Video S2).[26–28] The suggested dose is 100 U of Dysport™ or 20–30 U of BOTOX® every 3–6 months.

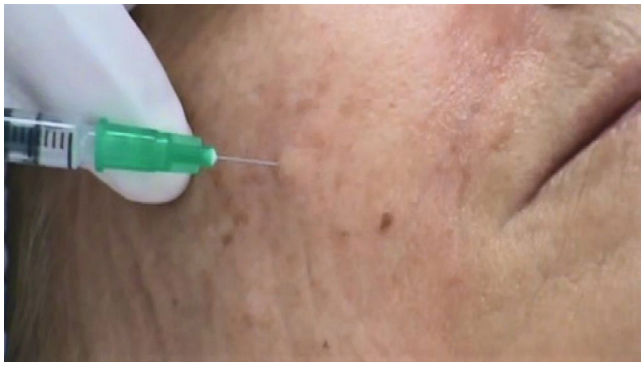

FIGURE 4 Intradermal injection in the jugal area for Rosacea treatment

3.7 | Perioral area

Excess show of the gums when smiling can cause what is known as a gummy smile, a benign condition yet esthetically unfavorable among those who have it. Off-label BTX administration focuses on relaxing the levator labii superioris alaeque nasi and the depressor septi nasi muscles. Upper and lower lips vertical lines, also referred to as 'barcode' lines, can also be treated as superficial as the needle bevel allows.[29] The suggested dose is 6–10 U of Botox distributed in 1 or 3 injection points every 3–6 months.

3.8 | Chin

The hypertrophic depressor anguli oris muscles can be treated by injecting BTX in one point on each side of the chin, alleviating what some refer to as a downturned smile. In this off-label indication, it is optimal to inject 1 cm away from the modiolus (corner of the mouth), ideally pinching the muscles. Since the smile can be affected by this treatment, this should be considered an advanced injection site.[30] The suggested dose is 2–4 U of BOTOX® every 3–6 months.

A hyperactive mentalis muscle causes an unaesthetic appearance of the chin known as a cobblestone chin. Off-label treatment with BTX can be achieved by injecting in a midline point 0.5–1 cm above the menton.[29] The suggested dose includes 4–8 U of BOTOX® every 3–6 months.

3.9 | Neck

The horizontal necklines and vertical bands that appear on the neck with aging are a common cause of concern to our patients, leading them to seek rejuvenation of the area. The off-label microbotox

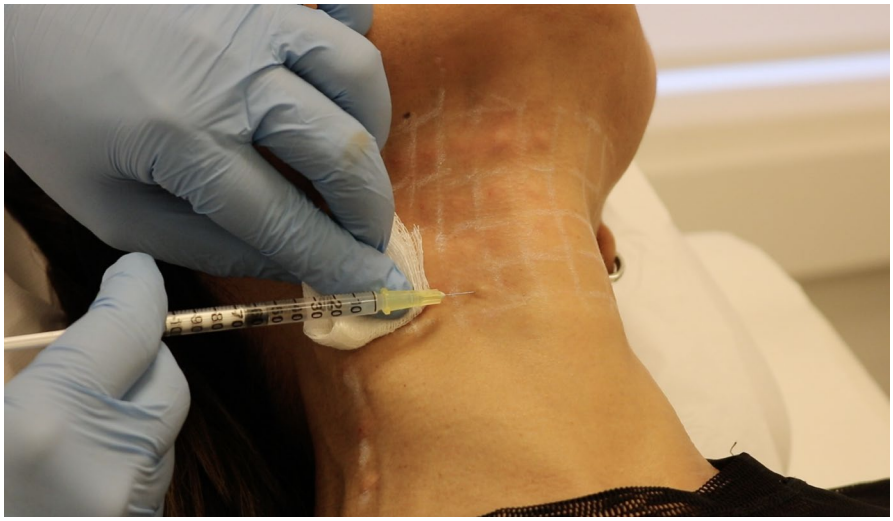

FIGURE 5 Microbotox being injected in the cervical area to decrease the appearance of horizontal neck lines

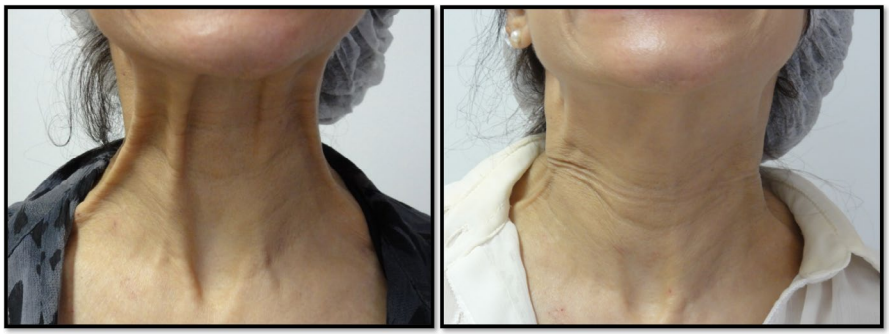

FIGURE 6 Before and after platysmal bands treatment with botulinum toxin

technique can be used to significantly improve neck appearance. A diluted toxin is injected into the overlying skin targetting both the superficial muscular layer fibers attached to the skin (Figure 5). BTX is injected in a mesh-like pattern 1 cm distance per injection along the anterior neck. (Video S3).[30] The suggested dose for this application is 20–28 units BOTOX® per ml for a total of 2 ml used every 6–10 months.

The platysma is a thin muscle that originates from the fascia overlying the pectoralis and deltoid muscles and extends to the neck and jawline.[31,32] De Castro describes three anatomical platysma variation patterns where 10% have no muscle decussation (type III) and type I/II have some muscle decussation level.[28] Where the muscle fibers do not decussate, the free medial edges create platysmal bands, an esthetically distressing appearance. Not all patients' necks are suitable for chemodenervation treatment.[33] Thus, proper patient evaluation is paramount, and parameters such as skin laxity, skin tone, and lipodystrophy should be considered before therapy, as proposed by the algorithmic approach from Rohrich et al.[34] When appropriate, the off-label treatment approach with BTX should be direct band injection (Figure 6) at 1 cm intervals along with the muscle (Video S3).[33] The suggested dose is 3–6 units BOTOX® per injection site. Every 6–10 months.

3.10 | Axilla

The axilla is a very common site for hyperhidrosis. Focal hyperhidrosis is initiated by the cholinergic fibers of the sympathetic nervous system innervation to the eccrine glands.[35] Hyperhidrosis has a negative psychosocial effect on patients.[32] Patients can be assessed using the Hyperhidrosis Disease Severity Scale (HDSS) to rate severity and examine treatment success. HDSS score of 1–2 should ideally start with antiperspirants containing aluminum chloride or iontophoresis before neurotoxin injection. Failure of antiperspirants or higher HDSS score can be considered for neurotoxin injection. The mechanism of action of neurotoxin injected intradermally to treat hyperhidrosis (Figure 7) is inhibition of ACh release at the neuromuscular junction of the eccrine sweat glands.[36] The suggested dose is 3–4 units BOTOX® every 1.5–2 cm to a total of 50–100 units per axilla repeated every 6–10 months.[34]

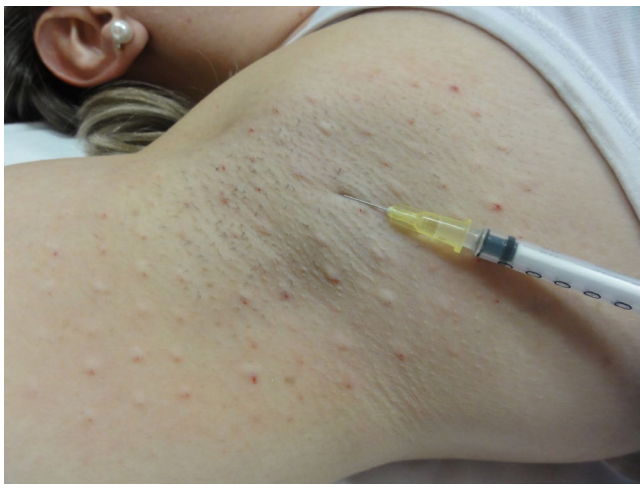

FIGURE 7 Intradermal injection in the axilla area for hyperidrosis treatment

3.11 | Palmar and plantar areas

As in axillary focal hyperhidrosis, the treatment strategy for palmoplantar hyperhidrosis relies on the HDSS score. If a patient presents with palmoplantar hyperhidrosis, it is recommended to treat the palms initially. Frequently following palmar treatment, a reduction in plantar hyperhidrosis is noted.[36,37] The suggested dose includes 3–4 units BOTOX® every 1 cm to a total of 100–150 units per palm (Figure 8) and 150–200 units per foot sole (Video S4) repeated every 6–10 months.[36,37]

3.12 | Breast

Breast reconstruction animation deformity may occur in both subpectoral and latissimus dorsi muscle breast reconstruction. Also, animation deformity can be seen after subpectoral breast augmentation.[38] Neurotoxin injection was suggested as an off-label alternative to surgical nerve denervation to relieve the deformity temporarily. The recommended treatment consists of injecting intradermally over the contracting breast. The upper and lower portions

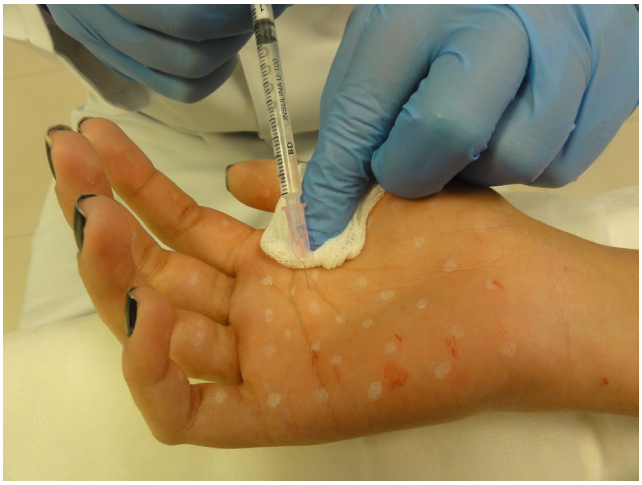

FIGURE 8 Palmar marking and injection of botulinum toxin for hyperidrosis treatment

of the breast are targeted.[39] The suggested dose is 100 units of BOTOX® diluted within 5 ml of normal saline injected every 1 cm, repeated every 3–6 months.

3.13 | Calf

As in masseter hypertrophy, gastrocnemius hypertrophy is an esthetic concern for some patients seeking the western beauty ideal of long slender legs. Hypertrophy is common in Asian females and poses a psychosocial burden on the patients.[40] For this off-label indication, the suggested dose is 300 units of Dysport™ or 75–100 units of BOTOX® per treatment. Further data are needed to elucidate concrete conclusions on the efficacy of this approach.

4 | DISCUSSION

Today, BTX is FDA-approved for 11 therapeutic indications, including blepharospasm, overactive bladder, chronic migraine, incontinence due to a neurologic condition, cervical dystonia, spasticity, and severe axillary hyperhidrosis in addition to cosmetic indications such as severe glabellar and moderate to severe lateral canthal lines. Off-label uses of BTX are often indicated as well. In some cases, effects are not entirely understood, as is the point in androgenetic alopecia and rosacea, which demands further investigation and studies with larger samples.[7,19]

Since BTX is no longer patent-protected, the number of available products has been increasing, and it has been used in large doses for a wide variety of indications, such as the recent description of calf hypertrophy treatment.[36] In recent years, it has been suggested that antigenicity of BTX-A may lead to failure of therapy due to the patient's immune response.[2] However, cosmetic use dosage, especially on the face and neck, is typically much lower than the ones used to treat large muscles and neurological disorders.[2] To date, there is no evidence that esthetic treatments on the face and neck lead to BTX-A antibody formation or that antibodies formed in patients treated with large doses are responsible for clinical failure of treatment.

5 | CONCLUSION

Botulinum neurotoxin is one of the most versatile and widely used medical products in the world. Our review focused on the plastic and dermatological uses of botulinum neurotoxin currently supported by published data. Even so, for some of the more recent applications, quality data are lacking. Further research is needed.

DISCLOSURE

Ricardo Frotta Boggio is a member of the speakers' bureau for Allergan, Inc. Videos and pictures of procedures were made using Botox, Allergan Inc., and were not donated by the company. All patients pictured and filmed have given their written consent for documentation and publishing.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to report.

AUTHOR CONTRIBUTION

Friedman Or MD contributed the introduction anatomical preface and conclusions. Roei Singolda, MD and Adriano Mesquita Bento, MD involved in review of literature and section write-up. Joseph N. Mehrabi - Joe made the final revision of the text. He re-verified the literature review and added references. Editing a review is substantial work. Ofir Artzi MD and Ricardo Frotta Boggio, MD, PhD contributed the clinical perspective, patients, and videos. None of the authors have any conflicts of interest to report.

INFORMED CONSENT

All the patients signed informed consent forms for the treatments and publication of images for scientific purposes.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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