Update on botulinum toxin and dermal fillers
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Purpose of review
The art and science of facial rejuvenation is an ever-evolving field of medicine, as evidenced by the continual development of new surgical and nonsurgical treatment modalities. Over the past 10 years, the use of botulinum toxin and dermal fillers for aesthetic purposes has risen sharply. Herein, we discuss properties of several commonly used injectable products and provide basic instruction for their use toward the goal of achieving facial rejuvenation.

Recent findings
The demand for nonsurgical injection-based facial rejuvenation products has risen enormously in recent years. Used independently or concurrently, botulinum toxin and dermal filler agents offer an affordable, minimally invasive approach to facial rejuvenation.

Summary
Botulinum toxin and dermal fillers can be used to diminish facial rhytides, restore facial volume, and sculpt facial contours, thereby achieving an aesthetically pleasing, youthful facial appearance.

Keywords
botulinum toxin, dermal fillers, facial rejuvenation

Introduction
Facial rejuvenation involves a spectrum of interventions, ranging from topical cosmetic products to surgical tissue manipulation. Botulinum toxin and dermal filler injections fall somewhere in the middle of this spectrum. Used alone or in conjunction with other modalities, botulinum toxin and dermal filler products play an important role in achieving a youthful, aesthetically pleasing facial appearance.

Background
Produced in nature by the Gram-positive rod \textit{Clostridium botulinum}, botulinum toxin is nature’s most potent exotoxin. Through research efforts over the past 30 years, medicine has harnessed the powerful toxin for use in a variety of therapeutic and aesthetic settings. Therapeutic potential was first recognized in the 1970s when Scott [1] used botulinum toxin to treat strabismus in monkeys. Scott, thereafter, produced botulinum toxin type A commercially under the trade name ‘Oculinum’ (Allergan, Inc., Irvine, California, USA), which gained the US Food and Drug Administration (FDA) approval in 1989 for treatment of dystonias [1]. Allergan purchased the rights to produce botulinum toxin-A (BTX-A) in 1991, and changed the name to the familiar moniker ‘BOTOX’ (Allergan, Inc.). In 2000, botulinum toxin-B (BTX-B) was approved for treatment of cervical dystonia under the trade name Myobloc (Elan Pharmaceuticals, Dublin, Ireland). Since its initial FDA approval, the scope of botulinum toxin has expanded to include treatment of a variety of spastic disorders, pain syndromes, hypersecretory conditions, and aesthetic concerns [2,3]. Botulinum toxin is currently FDA approved for treatment of over 20 conditions, and is commonly used ‘off-label’ for many more worldwide [2] (Table 1).

Origin, structure, and mechanism
Botulinum toxin is an exotoxin produced by the Gram-positive rod, \textit{C. botulinum}. The toxin is a disulfide-linked 50 kDa light chain/100 kDa heavy chain complex, bound to a variety of nontoxin stabilizing proteins [4]. Seven distinct toxin serotypes (A–G) exist in nature, each produced by a different strain of \textit{C. botulinum} [5]. Types A and B are commercially produced as they possess properties making them most clinically advantageous [6]. The toxin functions by inhibiting acetylcholine release at the neuromuscular junction, resulting in flaccid paralysis of targeted muscles. Toxin serotypes A and B differ in their binding site and target molecules in the presynaptic nerve terminal [7,8]. These small differences are clinically relevant, allowing alternative toxins to be employed in the event of treatment failure with a particular agent [9].
Table 1 | FDA-approved indications for botulinum toxin

<table>
<thead>
<tr>
<th>Formulation</th>
<th>FDA-approved uses</th>
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<tbody>
<tr>
<td>BOTOX</td>
<td>Upper limb spasticity</td>
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<td>Cervical dystonia</td>
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<td>Primary axillary hyperhidrosis</td>
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<td>Facial dystonias and strabismus</td>
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<td>Glabellar rhytides</td>
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<td>Dysport</td>
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<td>Glabellar rhytides</td>
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<td>Myobloc</td>
<td>Cervical dystonia</td>
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Available formulations of botulinum toxin type A

There are currently three available formulations of botulinum toxin type A, two of which are approved for use in the United States.

BOTOX (900 kDa)

Approved for use in dystonias in 1989 and BOTOX Cosmetic for cosmetic use in 2002, BOTOX is the most well studied of the type A botulinum toxins. BOTOX is distributed as a vacuum-dried powder that requires reconstitution with 0.9% (or physiologic) normal saline. Allergan packaging recommends reconstitution with nonpreserved saline, requiring use within 4 h. However, several studies have demonstrated no reduction in clinical efficacy [10,11], duration of action [11,12], or degree of paralysis measured electrophysiologically [13], when reconstituted with preserved saline and refrigerated up to 2 weeks. In practice, many clinicians use preserved saline and refrigerate BOTOX for use up to 7–10 days after reconstitution as per packaging recommendations. As with BOTOX, studies [10,17] have shown safety and efficacy when used beyond 2 weeks [11,15].

Dysport (500/900 kDa)

Approved for cosmetic use in the USA in April 2009, Dysport (Allergan, Inc.) has been used in over 65 countries worldwide since 1991 [16]. Dysport is a type A botulinum toxin that differs from BOTOX in purification methodology. It is distributed as a lyophilized powder requiring reconstitution with nonpreserved saline and use within 8 h of reconstitution as per packaging recommendations. As with BOTOX, studies [10,17] have shown safety and efficacy when used beyond 2 weeks after reconstitution with preserved saline.

Dilution

Dilutions reported in the BOTOX literature range from 10 to 100 U/ml, all of which demonstrate similar clinical efficacy and duration of effect [6,36]. Of note, higher concentrations (lower volumes) allow more precise delivery to smaller muscle groups, have less tendency toward diffusion to unintended areas, and distort local architecture to a lesser extent, resulting in less painful administration [6,37]. Most practitioners, however, use 40–50 U/ml for facial rejuvenation purposes.

Dosing

Dosage must be individualized based on muscle mass of the treatment area. For this reason, women generally require fewer units in a given treatment area versus men [38]. While variability exists regarding starting dose, there is a trend toward using fewer units of BOTOX as patients and practitioners attempt to avoid a ‘frozen’ appearance and minimize complications. General guidelines for treatment doses as well as injection patterns for commonly treated areas are as follows:

1. Glabella: 15–30 units divided (women), 20–40 units divided (men) (Fig. 1);
2. Horizontal forehead rhytides: 10–20 units (women), 1500–25 units (men) (Fig. 2a and b);
Botulinum toxin type B

Only one formulation of botulinum toxin type B is commercially available at the present time.

Myobloc (700 kDa)

FDA approved for treatment of cervical dystonia in 2000, Myobloc differs from BOTOX and Dysport in molecular binding site and intracellular enzymatic mechanism of chemodenervation at the neuromuscular junction [8,39,40]. Relative potency is reported to be 50–100 U Myobloc : 1 U BOTOX [32]. It is dispensed as a ready to use liquid (pH 5.6) with a shelf life of 9 months unrefrigerated per 4 years refrigerated [41]. Onset of paralysis is quicker (~48h) and duration of effect shorter (6–10 weeks) versus botulinum type A preparations [42,43]. Given the pain of injection as a result of the acidic solution, and brevity of paralysis, most practitioners use BTX-A primarily, reserving Myobloc for instances of resistance/nonresponse (or treatment failure with) to BTX-A [44].

Dermal fillers

Volume enhancement utilizing autologous fat dates back well over a century. Introduction of bovine collagen products in the 1980s led to an explosion of dermal fillers as a result of improved longevity and reproducibility of clinical effect [45]. Immunologic concerns and limited duration of effect led to development of human and porcine collagen products. More recently, however, hyaluronic acid fillers have become the predominant product for cosmetic volume restoration, accounting for more than 85% of fillers used in 2008 [46**], given their favorable physical properties (biologically inert, stable, space-occupying, longlasting, reversibility with hyaluronidase [47]. The number of commercially available hyaluronic acid fillers is rapidly evolving. Products differ in the concentration of hyaluronic acid, particle size, percentage of hyaluronic acid cross-linking, cross-linking agent used, and relative stiffness. Higher percentage hyaluronic acid cross-linking yields a stiffer product, which resists biodegradation and provides a longer duration of effect [48]. Early hyaluronic acid fillers were derived from rooster combs, requiring skin testing prior to use. This drawback led to the development of biocompatible nonanimal stabilized hyaluronic acid (NASHA) fillers commonly used today.

Although ultra long-lasting fillers composed of calcium hydroxyapatite, silicone, polymethylmethacrylate (PMMA), and other synthetic materials are available, given the advanced injection technique necessary and potential for complications [49,50], further details will not be discussed within the context of this article. Worthy of mention, however, is the fact that although increased duration of efficacy is generally a desirable characteristic of fillers, permanent products may lead to unsightly bumps and ridges as fat atrophy occurs with normal facial aging.

General principles

Regardless of trade name, products with smaller particles (softer consistency) are most useful for superficial injection to address fine lines, whereas larger particle (stiffer) hyaluronic acid fillers are best suited for deeper injection to treat volume loss and deep rhytides [50]. This approach achieves optimal outcomes and minimizes potential complications such as beading of larger particle fillers injected into the superficial dermis [51]. Layering multiple products is a useful approach to areas requiring both volume enhancement and fine wrinkle reduction. In general, superficial ‘fine-line’ products last approximately 6 months or more, whereas larger particle products range 6–12 months.
Figure 2 Treatment of transverse forehead lines

(a) Treatment of transverse forehead lines: Injections should be performed at the ‘equator’ of the brow midway between the brow cilia and hairline. Typical injection doses consist of 5 units of BOTOX or 15 Dysport units to each area indicated with a black ‘X’. Centrally, the frontalis muscle contains fewer muscle fibers and may only require 2.5–5 BOTOX units or 7.5–15 Dysport units indicated with a gray ‘O’. Injections should be avoided in the lateral forehead to prevent brow ptosis. Illustration by Lauren Shavell of Medical Imagery. (b) Alternate treatment pattern for treatment of transverse forehead lines: Typical injection doses consist of 2.5 units of BOTOX or 7.5 Dysport units to each area indicated with a gray ‘O’. Injections should be avoided in the lateral forehead to prevent brow ptosis. Illustration by Lauren Shavell of Medical Imagery. Reproduced with permission from Lipham W.J. Cosmetic and clinical applications of BOTOX and dermal fillers, second ed., SLACK Inc., 2008 (Figs 8.15 and 8.16).

Figure 3 Treatment of obicularis rhytides or ‘crows feet’

(a) Two-injection technique for obicularis rhytides or ‘crow’s feet’: Each ‘X’ represents approximately 5 BOTOX units or 15 Dysport units per injection site. Illustration by Lauren Shavell of Medical Imagery. (b) Three-injection-site technique for obicularis rhytides or ‘crow’s feet’: Each black ‘X’ represents approximately 5 BOTOX units or 15 Dysport units per injection site. The lateral canthal angle injections consist of either 2.5–5 BOTOX units or 7.5–15 Dysport units represented by a gray ‘O’. Illustration by Lauren Shavell of Medical Imagery. Reproduced with permission from Lipham W.J. Cosmetic and clinical applications of BOTOX and dermal fillers, second ed., SLACK Inc., 2008 (Figs 8.23 and 8.25).
Preinjection anesthesia
As with botulinum toxin, preinjection anesthesia methodology varies widely among practitioners. Options include topical anesthetic creams, ice packs, chilled air, vapocoolants, and regional nerve block [52]. Of note, three NASHA fillers (Hydrelle (Coapt Systems Inc., Palo Alto, California), Juvederm XC (Allergan, Inc.), and Prevelle Silk ( Mentor Corporation, Santa Barbara, California) now incorporate lidocaine as a vehicle in the same syringe and recently gained FDA approval, whereas several other products are currently seeking approval [53,54]. Studies and direct clinical experience demonstrate that these hyaluronic acid/anesthetic combination products significantly reduce injection-related discomfort [55].

Injection technique
Dermal filler injection technique varies widely among practitioners and treatment area. Most products can be injected with a 30-gauge needle. Some products require a 27-gauge needle due to particle size (see package insert). Common techniques include anterograde linear threading, retrograde linear threading, and fanning. Linear threading is well suited for correction of well defined linear rhytides, whereas fanning is useful in areas of diffuse volume deficit. Although technique is largely a matter of personal preference, adhering to basic guidelines will minimize the likelihood of technique-related adverse events. Slow injection of small volumes minimizes local tissue trauma, which is responsible for the majority of acute adverse events including pain, redness, ecchymoses, and edema. Discontinuation of anticoagulants 7–10 days prior to treatment further minimizes these injection-site reactions [56]. Avoid injecting too superficially, which can result in a bluish discoloration of the treated area (commonly referred as the Tyndall effect). Following injection, gentle massage of the treatment area helps to distribute the product, minimizing a lumpy or beaded appearance. Cold compresses help to reduce discomfort and swelling [56,57].

Vascular compromise
The most feared complication of hyaluronic acid filler injection is soft tissue necrosis related to vascular compromise in the treatment area. This necrosis may occur via direct arterial embolization, venous obstruction, or local pressure-related mechanisms [50,58–60]. Necrosis may occur with any injection, but has been reported most often in the glabellar region. Signs include skin blanching, unexpected level of pain, or violaceous discoloration of the treatment area. Management includes cessation of injection, followed by aspiration of any filler product possible. Vigorous massage helps to distribute the filler load. If necessary, warm compresses and 2% nitroglycerine paste may be used to achieve local vasodilation. Local injection of hyaluronidase may also be of some benefit [56,57].

Combination treatment
Facial aging is a multifactorial process involving the accumulation of hyperdynamic and static rhytides, loss of skin elasticity, gravitational descent, and volume depletion [51]. Recognizing this, facial aesthetic medicine has shifted toward utilizing multiple treatment modalities to synergistically achieve three-dimensional facial rejuvenation [61]. Several studies have demonstrated that combination treatment with hyaluronic acid fillers and botulinum toxin achieves superior clinical outcomes and greater patient satisfaction versus either modality alone [62–64]. In addition, one study [65] reported that combination treatment nearly doubled the duration of clinical efficacy. Combination treatment recommendations vary by facial region due to the fact that the age process affects the anatomy of each region differently. As a general rule, benefits of botulinum toxin are best utilized in the upper face, whereas dermal fillers play a greater role in mid and lower facial rejuvenation.

Upper face
Ageing of the upper face predominantly results from repetitive small muscle movements producing hyperdynamic rhytides. Gravitational descent and volume loss contribute to ageing of the upper face to a lesser extent. Therefore, rejuvenation of this region typically focuses first on treatment with botulinum toxin, followed by soft tissue augmentation as necessary. A common approach involves treatment of hyperdynamic lines with botulinum toxin at the initial visit. During follow-up evaluation (~1 week later), residual static rhytides/deep folds, need for additional sculpting (particularly of the lateral brow), and generalized volume deficits can be addressed with dermal fillers. Judicious use of smaller particle/softer fillers is preferred for delicate superficial upper facial regions (i.e. crow’s feet, glabella), given a propensity toward a beaded appearance with larger particle/stiffer products [51]. Reasonable injection volumes are as follows:

1. Glabella: less than 0.25–0.5 ml (superficial injection, low volume) (Fig. 4);
2. Forehead rhytides: varies depending on length of rhytid;
3. Crow’s feet: 0.25 ml (Fig. 5).

Midface
Midface ageing is primarily a function of gravitational descent and volume loss giving dermal fillers a preferential role in rejuvenation of this region [66,67]. The malar projection is instrumental in determining midfacial topography. Its volume and contour influence the appearance of the nasolabial, nasojugal, and orbitomalar grooves. Therefore, many clinicians recommend first restoring the malar contour via submuscular or subdermal injection of a
suitable large-particle, highly crosslinked filler product. After achieving a desirable malar volume/contour, the need for additional treatment of the aforementioned folds can be addressed with conventional intradermal injections of fillers such as Restylane or Juvederm Ultra. Treatment of the infraorbital hollow (or tear-trough deformity) and nasojugal folds are more difficult, and should be performed by experienced injectors. Of particular note, care must be exercised to avoid injection posterior to the orbital septum, which exacerbates pseudoherniation of orbital fat, resulting in an aesthetically unpleasant (and difficult to reverse) result. Recommendations include slow, gentle injection of small aliquots of hyaluronic acid, followed by massage to distribute filler. Conservative initial treatment with reevaluation 2–4 weeks later for touch-ups reduces the risk of overtreatment. Suggested injection volumes for the mid face include the following:

1. Malar contour: 1–3 cm$^3$/side injected in the submuscular plane;
2. Nasolabial fold: 0.5–1.0 cm$^3$/side (Fig. 6);

Figure 4 Injection of hyaluronic acid filler to reduce the appearance of glabellar furrows using a linear threading technique

Figure 5 Injection technique for treating crow’s feet with linear threading

Figure 6 Linear threading injection technique for the treatment of nasolabial folds with hyaluronic acid

Figure 7 Correction of nasal tear-trough deformity by injecting Juvederm Ultra Plus in the preperiosteal plane (below the orbitalis oculi muscle)
(3) Nasojugal fold (tear trough): 1–2 cm³/side injected in the preperiosteal plane;
(4) Malar smile lines: 0.2–0.4 cm³/side (deep dermal/subdermal plane, layer with soft product for superficial static rhytides);
(5) Infraorbital hollow: 0.5–1.0 cm³/side (Fig. 7).

Lower face

Ageing in the lower face involves subcutaneous fat atrophy, volume loss, and accumulation of hyperdynamic rhytides around the mouth [67]. The lips are central to lower facial appearance, and hyaluronic acid fillers are well suited to restoring lost volume in addition to defining the vermilion border.

(1) Vermillion border: 1.0–2.0 cm³ (avoid overfill ‘duck lips’) (Fig. 8),
(2) Marionette lines: 1.0–2.0 ml (for both sides) (Fig. 9).

Conclusion

As demonstrated throughout this article, nonsurgical approaches to facial rejuvenation have become enormously popular among both patients and practitioners in recent years. Facial rejuvenation is comprised of a spectrum of interventions ranging from topical cosmetics to surgical restoration. Injectable products fall somewhere in the middle of the spectrum, offering dramatic aesthetic results for a moderate cost and require minimal posttreatment recovery time. Although beyond the scope of the present discussion, injectable products have shown promise when used in conjunction with surgical approaches to facial rejuvenation as well. Limiting muscular contraction with preoperative botulinum toxin injection reduces tensile forces imposed on healing wounds. This allows meticulous wound closure using finer sutures, hence limiting postoperative scarring [68–70]. The present article serves as a general conceptual outline regarding the use of injectable products to achieve facial rejuvenation. Certainly, every patient warrants treatment approaches tailored to their specific situation, and when questions arise, specific recommendations should be sought from one’s more experienced colleagues.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 414).

1 Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. Ophthalmology 1980; 87:1044–1049.


This study discusses the dosing and injection patterns for cosmetic use of Dysport.


This study establishes safety and efficacy of botulinum toxin A reconstituted with preserved saline and stored for 2 weeks.


This paper is a good summary of available hyaluronic acid products and their properties.


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