NEUROMODULATORS AND INJECTABLE FILLERS

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INTRODUCTION

The use and number of injectable agents for cosmetic facial rejuvenation and reshaping continues to increase around the world. According to the 2014 American Society for Aesthetic Plastic Surgery (ASAPS) Cosmetic Surgery National Data Bank Statistics,1 more than 3.5 million botulinum toxin type A (BoNTA) and more than 1.6 million hyaluronic acid (HA) injection procedures were performed in 2014. For physicians and extenders combined, the number of BoNTA injections tops 4.6 million and HA injections are more than 2 million. The use of BoNTA accounted for more than 1.1 billion dollars in expenditures in 2014, with a 5407% increase since 1997.1 With increased comprehension of aging and the associated loss of volume of soft tissue and bone, the use of injectables is no longer limited to wrinkles alone. Wrinkles are sometimes a manifestation of volume loss; therefore, injectable agents can be used in several different roles.2−4 Injectable products and their literature are rapidly expanding and evolving. In this issue of Selected Readings in Plastic Surgery, we present neuromodulators and injectables fillers, review the current products approved by the United States Food and Drug Administration (FDA), and provide an overview of the clinical uses.

HISTORY

The history of tissue augmentation began when Neuber5 used autologous free fat from arms to reconstruct depressed facial defects in 1893 (Fig. 1). The first cosmetic injection was performed by Gersuny6 in 1899. He injected paraffin into a scrotum as a testicular prosthesis to correct the cosmetic deformity after testicular resection for advanced tuberculosis. Injectable paraffin and mineral oil were popular in the United States (US) and Europe until about 1920. Miller,7 in his 1926 book, Cannula Implants and Review of Implantation Technics in Esthetic Surgery, described the use of various materials, including “bits of braided silk, bits of silk floss, particles of celluloid, gutta percha, vegetable ivory, and several other insoluble foreign materials,” injected into the facial tissues to correct depressions, pits, and lines.8 Liquid silicone became popular in the 1940s and has been associated with numerous complications.9,10 Modern autologous fat transplantation emerged with the evolution of liposuction. In 1986, Illouz11 presented a report on the reinjection of fat from liposuction. Klein and Elson12 detailed the history of soft-tissue augmentation in 2000.
<table>
<thead>
<tr>
<th>Year</th>
<th>Injectable Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893–1920s</td>
<td>• Fat grafting</td>
</tr>
<tr>
<td>1900–1920s</td>
<td>• Paraffin oil</td>
</tr>
<tr>
<td>1940s</td>
<td>• Liquid silicone</td>
</tr>
<tr>
<td>1980s</td>
<td>• Fat grafting revival</td>
</tr>
<tr>
<td>1981</td>
<td>• Bovine collagen (Zyderm)</td>
</tr>
<tr>
<td>2002</td>
<td>• OnabotulinumtoxinA (Botox Cosmetic)</td>
</tr>
<tr>
<td>2003</td>
<td>• Human-derived collagen (CosmoDerm)</td>
</tr>
<tr>
<td>2004</td>
<td>• Hyaluronic acid (Hylaform, Captique)</td>
</tr>
<tr>
<td>2006</td>
<td>• Hyaluronic acid (Juvéderm Ultra, Juvéderm Ultra Plus, Elevess)</td>
</tr>
<tr>
<td>2007</td>
<td>• Perlane</td>
</tr>
<tr>
<td>2008</td>
<td>• Hyaluronic acid (Prevelle Silk)</td>
</tr>
<tr>
<td>2009</td>
<td>• AbobotulinumtoxinA (Dysport), poly-L-lactic acid (PLLA) Sculptra Aesthetic</td>
</tr>
<tr>
<td>2010</td>
<td>• Juvéderm Ultra Plus XC/ Ultra Plus XC, Restylane-L, Perlane-L</td>
</tr>
<tr>
<td>2011</td>
<td>• Xeomin, Belotero</td>
</tr>
<tr>
<td>2013</td>
<td>• Juvéderm Voluma XC</td>
</tr>
<tr>
<td>2014</td>
<td>• Restylane Silk</td>
</tr>
<tr>
<td>2015</td>
<td>• Radiesse Plus</td>
</tr>
</tbody>
</table>

**Figure 1.** Evolution of injectables in the US. *, no longer available.
THE IDEAL INJECTABLE

The ideal injectable should have a safe composition, easy delivery, excellent outcomes, and appropriate sensibility (Table 1). The material composition should not be antigenic, carcinogenic, teratogenic, or toxic. Administration of the injectable should be simple, reproducible, consistent, without migration, and safe. Patients should have minimal side effects, predictable outcomes, and minimal downtime. The product should also be practical, affordable, versatile, easily stored, and have a durable shelf life.13,14

DIFFERENTIATORS

Although no universally accepted classification system for fillers exists, product features and attributes differentiate one from another. The most common differentiators include the source of the product, mechanism of action, and length of duration. Duration of action is somewhat arbitrary in that it can be affected by multiple factors such as age, gender, animation characteristics, metabolism, and number of past treatments. In addition, injector technique affects the longevity of a product. Placing a product too deeply can dramatically shorten its duration simply because the results are not visible.

We present a review of the most commonly used FDA-approved soft-tissue fillers, categorized by product type. These include HA fillers, non-HA fillers, and permanent synthetic fillers (Table 2).

NEUROMODULATORS

Botulinum Toxin

Botulinum neuromodulators are produced by various strains of Clostridium botulinum with seven serotypes (A, B, C1, D, E, F, and G). Serotypes A and B have been isolated for clinical use.15 Botulinum toxin has a high affinity for uptake by cholinergic neurons, resulting in temporary chemo-denervation. It reduces muscular contractions by binding to receptor sites on presynaptic autonomic nerve terminals and temporarily inhibiting acetylcholine release at the neuromuscular junction via four steps: binding, internalization, translocation, and intracellular proteolysis (Fig. 2).16–18

Botulism poisoning was first described in 1817 by Kerner.19 The first therapeutic use of botulinum toxin was for the treatment of strabismus by Scott et al.20 in 1973. It has numerous medical uses, including the treatment of essential blepharospasm, migraines, and hyperhidrosis.21–23 The first cosmetic use of botulinum toxin is attributed to Carruthers and Carruthers,24,25 who noticed the incidental improvement of glabellar rhytides while treating ophthalmological disease. Cosmetic botulinum toxin use has been noted to improve first impression scores for dating success, attractiveness, and athletic success scales.26 Currently, three BoNTA-Type A and one botulinum toxin type B FDA-approved products are available.

BoNTA-ONA (Botox and Botox Cosmetic)

OnabotulinumtoxinA, known as BoNTA-ONA and previously known as BoNTA, is marketed as Botox and Botox Cosmetic (Allergan, Irvine, CA). When first studied, it was named Oculinum. Botox is FDA-approved for cervical dystonia, chronic migraine, urinary incontinence, severe primary axillary hyperhidrosis, strabismus, and blepharospasm. In 2002, it received FDA approval for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugators and/or procerus muscle activity in adult patients younger than 65 years. In 2013, the FDA granted approval of Botox Cosmetic for temporary improvement in the appearance of moderate to severe lateral canthus lines, known as crow’s feet, in adults.

According to the full prescribing information, Botox is contraindicated in the presence of infection at the proposed injection site(s) and in persons with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation. Caution is advised for patients with peripheral motor neuropathic diseases, amytrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton myasthenic syndrome).
### Table 1
The Ideal Injectable

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Nonantigenic, noncarcinogenic, nonteratogenic, nontoxic</td>
</tr>
<tr>
<td>Delivery</td>
<td>Simple, reproducible, consistent, nonmigratory, safe</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Minimal side effects, predictable outcomes, minimal downtime</td>
</tr>
<tr>
<td>Sensibility</td>
<td>Cost-effective, versatile, easily stored, durable shelf-life</td>
</tr>
</tbody>
</table>

### Table 2
United States Food and Drug Administration-Approved Neuromodulators and Injectable Fillers

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Company</th>
<th>Composition</th>
<th>Date of FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiesse Plus</td>
<td>Merz Aesthetics</td>
<td>Calcium hydroxylapatite + lidocaine</td>
<td>2015</td>
</tr>
<tr>
<td>Restylane Silk</td>
<td>Galderma</td>
<td>Hyaluronic acid + lidocaine</td>
<td>2014</td>
</tr>
<tr>
<td>Juvéderm Voluma XC</td>
<td>Allergan</td>
<td>Hyaluronic acid + lidocaine</td>
<td>2013</td>
</tr>
<tr>
<td>Belotero Balance</td>
<td>Merz Aesthetics</td>
<td>Hyaluronic acid</td>
<td>2011</td>
</tr>
<tr>
<td>Juvéderm Ultra XC</td>
<td>Allergan</td>
<td>Hyaluronic acid + lidocaine</td>
<td>2010</td>
</tr>
<tr>
<td>Juvéderm Ultra Plus</td>
<td>Allergan</td>
<td>Hyaluronic acid + lidocaine</td>
<td>2010</td>
</tr>
<tr>
<td>Restylane-L</td>
<td>Galderma</td>
<td>Hyaluronic acid + lidocaine</td>
<td>2010</td>
</tr>
<tr>
<td>Sculptra Aesthetic</td>
<td>Galderma</td>
<td>Poly-L-lactic Acid</td>
<td>2009</td>
</tr>
<tr>
<td>Prevelle Silk</td>
<td>Mentor</td>
<td>Hyaluronic acid + lidocaine</td>
<td>2008</td>
</tr>
<tr>
<td>Perlane</td>
<td>Galderma</td>
<td>Hyaluronic acid</td>
<td>2007</td>
</tr>
<tr>
<td>ArteFill</td>
<td>Suneva Medical, Inc.</td>
<td>Polymethylmethacrylate</td>
<td>2006</td>
</tr>
<tr>
<td>Hydrelle (Elevess)</td>
<td>Anika Therapeutics</td>
<td>Hyaluronic acid + lidocaine</td>
<td>2006</td>
</tr>
<tr>
<td>Juvéderm</td>
<td>Allergan</td>
<td>Hyaluronic acid + lidocaine</td>
<td>2006</td>
</tr>
<tr>
<td>Radiesse</td>
<td>Merz Aesthetics</td>
<td>Calcium hydroxylapatite</td>
<td>2006</td>
</tr>
<tr>
<td>Restylane</td>
<td>Galderma</td>
<td>Hyaluronic acid</td>
<td>2003</td>
</tr>
</tbody>
</table>
syndrome). Patients with neuromuscular disorders might be at increased risk for clinically significant effects, including severe dysphagia and respiratory compromise. Aminoglycoside co-administration can also potentiate the clinical effects.27

Botox is not recommended for use in children but has shown substantial benefit as an adjunct to treatment in children with cerebral palsy spasticity.28 Application of Botox is not recommended during pregnancy, and without adequate studies, it is considered to be in pregnancy category C. It is not known whether it is excreted in human milk.29 BoNTA precautions are as follows:

- Infection at injection site
- Known hypersensitivity

Botulinum toxin can spread or diffuse after injection. “Spread” refers to the process after the injection itself, which is related to technique, volume of injection, and needle size. This is fast and active. “Diffusion” refers to the process as toxin moves away from the injection site. This is slow and passive, taking several days.30 Remote migration of botulinum toxin to the central nervous system has been reported to occur in animal studies but has not been shown to occur in human study participants.31,32 Based on these findings, all FDA-approved botulinum toxin products include a box label warning of the possibility and complications of distant spread. Symptoms can include generalized muscle weakness, diplopia, blurred vision, eyebrow and/or eyelid ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. Such symptoms have been reported to occur hours to weeks after injection, and there have been reports of death. Hypersensitivity reactions including anaphylaxis, urticaria, soft-tissue edema, and dyspnea have also been reported.29

Antibodies to Botox have been reported and can lead to loss of treatment effect. Antigenicity is a concern regarding long-term use of toxin, and, although rare, several case reports have identified secondary resistance after multiple BoNTA injections.33,34 These reports support the use of botulinum toxin type B formulations, or Incobotulinum toxin (BoNTA-INCO) (Xeomin; Merz Aesthetics, Raleigh, NC), which does not have any bound proteins, as alternatives. Botox underwent a formulation change in 1997 to decrease protein content from approximately 25 ng/100 U to approximately 5 ng/100 U, which was found to result in a decrease in antibody formation from 9.5% to 1.2%.35,36
Common adverse events occur within the first week and are transient. The events include localized pain, infection, inflammation, tenderness, swelling, erythema, bruising, and local weakness. In 2003, Klein provided a review of the complications of botulinum toxin, most of which are related to poor injection techniques.

Botox is produced from the Hall strain of C. botulinum. One unit corresponds to the calculated median intraperitoneal lethal dose (LD$_{50}$) in mice. The human LD$_{50}$ is approximately 40 U/kg, or approximately 3000 U. Vials are available in 100 or 50 U. Each 100-U neuromodulator vial currently contains 0.5 mg of Albumin Human and 0.9 mg of sodium chloride, vacuum-dried without a preservative.

According to the package insert, Botox is to be reconstituted with 0.9% sterile, non-preserved saline before intramuscular injection at a concentration of 4 U/0.1 mL. The reconstituted solution should be clear, colorless, and free of particulate matter. After opening, the product should be stored in a refrigerator and used within 24 hours. Unopened vials can be refrigerated for up to 36 months.

Alam et al., in a prospective, double-blinded, randomized controlled trial, found significantly ($P < 0.001$) decreased patient discomfort at the time of injection with preserved compared with nonpreserved saline reconstitution. Carruthers et al. found no difference in efficacy or safety in a dose-dilution study in which 30 U was reconstituted in 1 to 10 mL. Hxssel et al. found that potency can be maintained for up to 6 weeks after reconstitution. The reconstitution, dilution, and storage are matters of personal physician preference.

**BoNTA-ABO (Dysport)**

AbobotulinumtoxinA, known as BoNTA-ABO, is a BoNTA formulation marketed as Dysport (Galderma, Fort Worth, TX) (Fig. 3). BoNTA-ABO has been used in the United Kingdom and other parts of Europe since 1991 and was FDA-approved in 2009 for cervical dystonia and temporary improvement in the appearance of moderate to severe glabellar lines associated with the procerus and corrugator muscle activity in adult patients younger than 65 years.

Rubin et al. and Baumann et al. summarized phase III clinical trials of the safety and efficacy of Dysport. Rubin et al., Kane et al., and Brandt et al. conducted multicenter, randomized, placebo-controlled, double-blinded studies. A series of open-labeled trials have concluded that single treatment, variable dosing, and multiple cycles of treatment with Dysport is well tolerated, has a safety profile comparable to that of placebo, and significantly improves glabellar lines compared with placebo. The median time to onset is 3 days, with results reported to last as long as 36 months. No tolerances have been described. In addition, Lawrence and Moy found no evidence of neutralizing antibodies in 1554 patients who received Dysport.

Dysport is produced from a different type A strain of bacteria, C. botulinum NCTC 2916, with different manufacturing processes and is not equivalent to Botox (Table 3). The units are specific to each product’s manufacturer. They have no relationship to potency and are not interchangeable.
Vials for cosmetic use contain 300 U (500 U for cervical dystonia), which appears as a powder cake at the bottom of the vial as opposed to Botox, which appears as dust at the bottom of the vial. Each vial contains 125 mcg of human serum albumin, 2.5 mg of lactose, with trace amounts of cow’s milk proteins. The mean toxin protein content is 4.35 ng per 500 LD50-unit vial. Contraindications are the same as for Botox with the addition of allergy to cow’s milk proteins.

According to the package insert, Dysport is to be reconstituted with 0.9% sterile, non-preserved saline with either 1.5 or 2.5 mL, resulting in a concentration of 10 U/0.05 mL and 10 U/0.08 mL, respectively. The reconstituted solution should be clear, colorless, and free of particulate matter. After opening, the product should be stored in a refrigerator and used within 4 hours.

An approximate conversion factor between Dysport and Botox might provide guidance and level of comfort for practitioners, but the products should be viewed as different products. One unit of Botox is approximately equivalent to 2.5 to 5 U of Dysport.

Lowe et al. used a 1:2.5 unit ratio and compared Botox (20 U) to Dysport (50 U) in a randomized, double-blinded study for the treatment of glabellar lines. The authors found a relapse incidence of 23% for Botox versus 40% for Dysport and concluded that Botox provided a significantly prolonged effect at 16 weeks (P = 0.04). Rzany and Nast plotted the results of different Dysport and Botox studies on the same graph and concluded that the response curves for both products are very similar (Fig. 4). Kassir et al. compared Dysport with Botox in a triple-blind, prospective, internally controlled study in 2013 for the treatment of facial rhytides using a dose ratio of 2.5:1 and 3:1 Dysport: Botox. The study concluded that Dysport had a faster time to improvement and longer duration of improvement compared with Botox for glabellar wrinkles and crow’s feet when used in these ratios. A single study reported successful treatment of masseter hypertrophy using 100 to 140 units of Dysport per side in 121 patients, with the majority requiring four to five injections over time.

Botox is exclusively 900 kDa, whereas Dysport is a mixture of smaller complex sizes, 300 to 900 kDa, with the core neurotoxin protein being 150 kDa. Concern regarding diffusion caused by the smaller complex size of Dysport over Botox has been disproved by Pickett, who showed that the complex dissociates immediately after injection, negating the effect of complex size. Two studies compared the diffusion of Dysport and Botox by measuring anhydrotic halos. Trindade de Almeida et al. used variable dose ratios and found Dysport to have a larger area of action in 93% of patients at all dose ratios. Hexsel et al. used a 1:2.5 dose conversion ratio and found no significant difference between action sizes. A 2:1 ratio of Dysport:Botox in a recent study resulted in a significantly greater diameter of effect for Dysport compared with Botox, although the difference was described as “clinically irrelevant” considering the difference was greater than individual variations in field effects. Recent data on the topic stems from a 2013 prospective, single center, randomized, double-blinded study of 19 patients. Each patient received 2 units of Botox on one side and Dysport on the other. When the same dose was administered on each side, Botox resulted in a greater field of diffusion; however, the clinical effect was statistically comparable for both products at the same dose.

BoNTA-INCO

BoNTA-INCO was FDA approved for the treatment of glabellar lines, blepharospasm, and cervical dystonia in 2011. With its first use in Germany, BoNTA-INCO is currently approved for use in more than 20 countries and is marketed under the trade names Xeomin (in the US, Canada, and Mexico) (Merz Aesthetics) (Fig. 5) and Bocouture outside of the US. The product is available in 100-U vials containing 0.6 ng total protein and 4.7 mg sucrose. It is the first formulation of BoNTA without complexing proteins. It was theorized that by eliminating complexing proteins, the predictability of
product spread and clinical effect would be enhanced; however, clinical and pharmacological studies have shown that the presence of complexing proteins does not influence diffusion of the products.\textsuperscript{70,71} Eliminating complexing proteins has, however, been shown to reduce antigenicity and to prevent or reduce host inflammatory response to injections.\textsuperscript{72,73} 

In 2010, an international, non-inferiority phase III clinical trial showed that 24 units of BoNTA-INCO was non-inferior to 24 units of Botox for treating moderate to severe glabellar lines.\textsuperscript{74} Adverse events and patient satisfaction are statistically comparable between Botox and BoNTA-INCO.\textsuperscript{75,76} 

When all three formulations of botulinum toxin were compared head to head in a 2013 randomized, double blinded, prospective study, BoNTA-INCO was found to have a faster onset of action and longer duration of effect compared with Botox at a 1:1 dose ratio and compared with Dysport at a 1:3 dose ratio.\textsuperscript{77} BoNTA-INCO showed a mean onset of effect at 3.02 days compared with 5.29 and 5.32 days for Botox and Dysport, respectively. No association was observed between time of onset and duration of effect.

According to the package insert, BoNTA-INCO should be reconstituted with 0.9% normal saline. Reconstitution using 2 to 2.5 mL per 100-U vial is commonly recommended.\textsuperscript{78} Once the vacuum has drawn the saline onto the vial, the vial must

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Type A Botulinum Toxin Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dysport</td>
</tr>
<tr>
<td>Vial size</td>
<td>300 U</td>
</tr>
<tr>
<td>Composition</td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td>4.35 ng</td>
</tr>
<tr>
<td>Albumin</td>
<td>125 μg</td>
</tr>
<tr>
<td>Other</td>
<td>2.5 mg of lactose</td>
</tr>
<tr>
<td>Type A strain</td>
<td>NCTC 2916</td>
</tr>
<tr>
<td>Complex weight</td>
<td>≥300 kDa</td>
</tr>
<tr>
<td>Preparation</td>
<td>Lyophilized</td>
</tr>
<tr>
<td>Clinical generalizations</td>
<td></td>
</tr>
<tr>
<td>Conversion</td>
<td>2.5 U</td>
</tr>
<tr>
<td>Onset</td>
<td>3–5 days</td>
</tr>
<tr>
<td>Spread</td>
<td>More</td>
</tr>
<tr>
<td>Duration</td>
<td>Same</td>
</tr>
</tbody>
</table>
be inverted two to four times. This is because the product is not freeze-dried and can therefore stick to the inside of the stopper and walls of the vial. The reconstituted product should be clear and colorless, not cloudy. Although all formulations of BoNTA must be refrigerated once reconstituted, Xeomin can be stored at room temperature for up to 36 months before reconstitution. Once reconstituted, it should be used within 24 hours.

RimabotulinumtoxinB (Myobloc)

RimabotulinumtoxinB is botulinum toxin type B marketed as Myobloc (Solstice Neurosciences, LLC, a subsidiary of US WorldMeds, LLC, Louisville, KY). In Europe, this product is known as Neurobloc. Myobloc was FDA-approved for cervical dystonia in 1995. When compared with Botox, Myobloc has an earlier onset of action by 1 to 3 days; a briefer duration of effect;70,81,82 less predictable results, possibly because of a greater radius of diffusion; and more discomfort at the time of injection, possibly caused by the lower pH value (pH value, 5.6) as compared with Botox (pH value, 7.3).57,83

SPECIAL TOPIC: HYPERHIDROSIS

In 2004, Botox received FDA approval for the treatment of severe axillary hyperhidrosis in patients older than 18 years after failed topical treatment.84

Figure 4. Comparison of results of 50 U of Dysport (blue lines) versus 20 U of Botox (black lines) injected to treat glabella wrinkles in five studies. The curves are notably similar. (Modified from Rzany and Nast.83)
Botox is also used off-label for the treatment of palmar hyperhidrosis. The basis of using Botox for hyperhidrosis stems from the physiology of eccrine glands: the sweat-producing glands present in high concentration in the axillae, palms, and soles. These glands are innervated by postganglionic sympathetic neurons that are stimulated by acetylcholine. Clinical diagnosis of hyperhidrosis requires at least 6 months of excessive sweating, with episodes occurring at least once per week, not occurring during sleep, beginning before the age of 25 years, impairing daily activities, and occurring in a symmetric and predictable pattern.

Currently, Level B evidence exists for the use of Botox and Dysport for the treatment of hyperhidrosis, Level C for Xeomin, and level U for Myobloc. Only Botox is FDA approved for this indication; Dysport and Xeomin are currently being used off-label in comparative studies. The use of botulinum toxin for axillary hyperhidrosis has been well established, with several double-blinded trials confirming the efficacy and safety of Botox, Dysport, and Xeomin. Dosing ranged from 50 to 100 U/axilla total for Botox, 120 to 250 U/axilla for Dysport, and 50 U/axilla for Xeomin. Duration of effect is generally 5 to 6 months but has been reported to last as long as 1 year in some studies using Botox. Lakraj et al. presented a detailed review of the clinical trials.

The use of botulinum toxins for palmar hyperhidrosis has also been well established, with several double-blinded studies confirming the efficacy and safety of Botox, Dysport, and Xeomin for the treatment of palmar hyperhidrosis. Intradermal injection of 2 to 2.5 U/site (total, approximately 100 U/palm for Botox or Xeomin and 120 U/palm for Dysport), with a small-gauge needle is currently recommended for palmar hyperhidrosis. In the noted studies, duration of effect ranged from 3 to 8 months for all botulinum formulations.

**FUTURE PRODUCTS**

A novel application of botulinum toxin is a topical formulation of the type A toxin, known as RT001, currently in development by Revance Therapeutics, Inc. (Newark, CA). The product is in phase III clinical trials for the treatment of crow’s feet. Its use for hyperhidrosis and migraine headaches has reached phase II clinical trials. Efficacy and safety of the product for the treatment of lateral canthal lines were assessed in a randomized, double-blind, placebo-controlled study in 2012. At the 4-week follow-up time point, 44% of the treated lateral canthal areas showed at least 2 points of improvement in the severity scale used by the investigator compared with 0% of those in the placebo group. No treatment-related adverse events were reported.

In September 2014, Alphaeon Corporation received FDA approval of its Investigational New Drug (IND) Application to conduct clinical trials for Evosyal, its botulinum toxin type A product. Evosyal is a 900 kDa neurotoxin molecular complex with high purity. Enrollment in the clinical trials is expected to begin in January 2015.
TREATMENT RECOMMENDATIONS

Considering the substantial variations in techniques, guidelines in the literature, and personal experiences, Carruthers et al.\textsuperscript{42,103} convened in 2004 to develop consensus guidelines for best practices, which were updated in 2013.\textsuperscript{78} The recommendations are recapitulated in Table 4\textsuperscript{56,78,103} and Figure 6. After intramuscular treatment, most areas should not be manipulated for several hours.\textsuperscript{42} The duration of activity should be expected to last approximately 3 to 4 months. Fagien\textsuperscript{104} and Carruthers and Carruthers\textsuperscript{105} presented a report of pretreatment with Botox 1 to 2 weeks before laser resurfacing, which might improve results by eliminating the hyperfunctional component during healing.

Upper Face

The upper face is the most common site to receive neuromodulator injections. The literature regarding treatment to the upper face, particularly the glabellar complex, is extensive. The Botox Cosmetic package insert\textsuperscript{29} recommends five injection sites for the glabellar complex and vertical frown lines. Men, in general, might require more injection sites and more product, considering the male muscle mass is larger, on average.

For horizontal forehead lines, the goal should be to weaken but not completely paralyze the frontalis muscle. Usually, four to six injection points are used. Overtreatment of the frontalis will result in brow ptosis or asymmetry and can be avoided by keeping injections no closer than 1 to 2 cm above the bony orbital rim at the lateral corrugators and staying above the first horizontal line above the brow. Lower doses of neuromodulator should be used in older patients to avoid brow ptosis.\textsuperscript{103} Injections should be lateral enough to avoid a “quizzical” eyebrow appearance. To avoid upper eyelid ptosis from diffusion through the septum to the levator muscle, injections should be avoided under the mid brow.\textsuperscript{42}

Lateral orbital wrinkles, commonly known as crow’s feet, are addressed by injections to the lateral orbital portions of the orbicularis muscle. Injections range from two to five per side and should be performed superficially. Diplopia, ectropion, and smile asymmetry can occur. These conditions can be avoided by injecting 1 cm outside the bony orbit, thus avoiding the lateral rectus muscle. Also, to avoid the zygomaticus, injections should not approach the inferior margin of the zygoma.\textsuperscript{37}

Midface

Contraction of the nasalis across the bony dorsum results in “bunny lines” at the nasal radix. Injection into the nasalis as it transverses the nasal bone should be performed superficially to avoid bruising. Injections should also stay high on the lateral nasal wall, above the nasofacial groove, to avoid the levator labii superioris, which would result in upper lip ptosis.\textsuperscript{58}

Neuromodulators can also be used for dynamic nasal tip ptosis. Dayan and Kempiners\textsuperscript{106} injected 5 U of Botox into each depressor septi nasi and 3 U into each levator labii superioris alaeque nasi muscle, after which the excessive action of these muscles was attenuated at 2-week follow-up. The nasal tip became less ptotic with maximal smile effort.

Lower Face

The perioral area is essential to the lower face, and inappropriate treatment can cause significant dysfunction, such as drooling, speech difficulties, and oral incompetence. Knowledge of the anatomy and patient selection are critical, especially for those who use their lips as a profession (e.g., musicians, singers, public speakers). Treatments should be conservative, avoiding the corners for drooping and drooling and the midline upper lip for flattening. The number of injection sites varies considerably.\textsuperscript{42}

The depressor anguli oris pulls down the corner of the mouth in opposition to the zygomaticus muscles. Palpation of the muscle should be performed, and medial or high injections should be avoided. Injections too high on the lips can affect the orbicularis oris and worsen asymmetry. This can be prevented by not injecting higher than halfway between the lips and the mandible.\textsuperscript{103}
**Table 4**

Recommendations for the Use of Botulinum Toxin Type A\(^{56,78,103}\)

<table>
<thead>
<tr>
<th>Region/Target Muscle(s)</th>
<th>Usual No. of Injection Points</th>
<th>Total Dose (Botox/Xeomin)</th>
<th>Total Dose (Dysport)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper face</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical frown lines, glabellar complex (procerus, depressor supercilii, corrugator supercilii)</td>
<td>5–7; men might require more sites</td>
<td>Women: 10–30 U Men: 20–40 U</td>
<td>40–80 U</td>
</tr>
<tr>
<td>Horizontal forehead lines (frontalis, but consider interactions with procerus, corrugators, and orbicularis oculi in overall facial shape)</td>
<td>4–6; more or fewer might be required based on anatomic and aesthetic evaluations</td>
<td>Women: 10–20 U Men: 10 to &gt;20 U</td>
<td>20–50 U</td>
</tr>
<tr>
<td>Lower eyelid (junction between tarsal and orbital orbicularis)</td>
<td>1</td>
<td>Women: 0.5–2.5 U</td>
<td>1–6 U</td>
</tr>
<tr>
<td>Crow’s feet (lateral portions of the lateral orbicularis)</td>
<td>2–5 per side (higher in selected patients)</td>
<td>Women: 8–16 U Men: 20–30 U</td>
<td>16–40 U</td>
</tr>
<tr>
<td><strong>Midface</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radix (nasalis)</td>
<td>1–2</td>
<td>2–4 U</td>
<td>6–15 U</td>
</tr>
<tr>
<td>Nasal tip (depressor septi nasi, levator labii superioris alaeque nasi)</td>
<td>2–4</td>
<td>3–5 U to each muscle</td>
<td>10–15 U</td>
</tr>
<tr>
<td><strong>Lower face</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioral area, orbicularis oris</td>
<td>2–6; 4 sites, 1 site per lip quadrant</td>
<td>4–5 U</td>
<td>10–20 U</td>
</tr>
<tr>
<td>Depressor anguli oris</td>
<td>1–2</td>
<td>2–3 U (2.5 U/side)</td>
<td>6–10 U</td>
</tr>
<tr>
<td>Dimpled chin (peau d'orange), mentalis</td>
<td>1–2 (start with 1 midline or 2 symmetrical lateral injections)</td>
<td>4–5 U</td>
<td>10–20 U</td>
</tr>
<tr>
<td>Neck, platysmal bands, platysma</td>
<td>2–12/band</td>
<td>&lt;10 U/band</td>
<td>40–80 U/band</td>
</tr>
<tr>
<td>Masseteric hypertrophy</td>
<td>1–2 sites in muscle</td>
<td>25–30 U/side</td>
<td>100–300 U/side</td>
</tr>
</tbody>
</table>

*Dosages reflect 1:1 ratio for onabotulinumtoxin and incobotulinumtoxin; for abobotulinumtoxin, a conversion factor of 2:1 or 2.5:1 is recommended.*
The dimpled chin, peau d’orange, can be controlled with conservative injection into the mentalis. The mentalis protrudes the lower lip and wrinkles chin skin. Injection into the mentalis in addition to soft-tissue augmentation is recommended. When treating the mentalis, it is important to avoid the depressor labii muscles.103

Platysmal bands can be softened with neuromodulators in patients with good skin elasticity and minimal fat descent. Conservative injections at least 1 cm apart on each band while grasping the bands or by using electromyographic guidance will result in more accurate placement. Judicious treatment should be performed to avoid dysphagia or voice changes.107 Oral anticholinesterase (pyridostigmine), up to 60 mg, can be used to counteract the side effects.103

Excessive gingival display, gummy smile, can be addressed with small amounts of neuromodulators into the lip elevators. Botox injection of 1 to 2 U per side or 2 to 3 U in the depressor septae are conservative options.103 Other studies present the results of injections into the levator labii superioris, zygomaticus minor, and orbicularis oris.108,109

Hypertrophic masseter reduction has been successful with neuromodulators. Injections should be low, just above the mandible, with one to two sites per side.103 Injection of 25 to 30 U of Botox per side has been shown to be efficacious, lasting up to 6 months (Table 4).56,78,82,103,110,111

INJECTABLE FILLERS

The use of soft-tissue fillers has greatly increased during the past 10 years, with more than 3.2 million injectable filler procedures performed by physicians and physician extenders in 2013.1 The number of products continues to increase as well, with each having subtle biochemical differences. This makes it imperative but challenging for the cosmetic clinician to remain up-to-date on the literature. Rohrich et al.,112 in 2011, and Cohen et al.,113 in 2013, provided in-depth systematic reviews of the literature regarding these products.

Collagen Fillers

Aging causes a reduction in the collagen content of the skin by 1% per year.114 Bovine collagen was the first nonautologous filler to be approved by the FDA, in 1981, for the treatment of wrinkles, smile and frown lines, acne, and postsurgical scars.115 Because of the availability, success, and longer effect of HA fillers, the manufacture of collagen-based fillers has largely been discontinued and the products are no longer available in the US. Animal-based collagen fillers required double skin testing, and most collagen filler products lasted 3 to 6 months, with 75% loss of correction occurring by 6 months.14,116−121 The following collagen filler products are no longer available in the US: Zyderm 1 and 2 (Allergan),
Zyplast (Allergan), CosmoDerm 1 and 2 (Allergan), Cosmoplast (Allergan), Evolence (Ortho Dermatologies, Skillmann, NJ).

HA Fillers

HA is a glycosaminoglycan biopolymer that is a natural component of connective tissue in living organisms. It is chemically the same for all species and has reduced risk for allergic reactions, so skin testing is not required with this product. HA is hydrophilic and provides a structural matrix to retain moisture within the dermis, where collagen can develop. One gram of HA can bind up to 6 L of water. HA products were developed as an alternative to collagen because of their longer duration of effect and lower potential for hypersensitivity reactions, a reported rate of 0.6% to 0.8%. Animal-based HA fillers derived from rooster combs are available but no longer marketed in the US; we therefore limit our discussion to non-animal-based HA.

FDA-approved HA fillers for aesthetic use are derived from Streptococcus equi. Hyaluronic gels, known as hylans, are cross-linked at varying degrees to improve stability and increase longevity. Naturally occurring HA has a half-life of approximately 20 h. Hyaluronic gels are 95% water by weight. Dynamic viscosity, a unique attribute of hyaluronic gels, refers to decreasing viscosity as shear rate increases. At the time of injection, high-shear-rate hyaluronic gels pass through needles more easily. At the time of removal of shearing forces, the viscosity increases and the gel thickens at its implanted site, minimizing migration. Another unique property of hyaluronic gels is isovolemic degradation. As the product degrades, the remaining HA binds more water, such that the overall volume remains the same. This process can maintain 95% of the initial filling volume until all of the material is resorbed.

The distinction between HA products is related to their molecular composition and biophysical properties. The viscosity and elastic modulus (G’) of the HA dictate the physiological behavior of the gel. Viscosity refers to the ability of a gel to resist shear forces. For example, peanut butter is highly viscous compared with mustard in that it requires more force to spread peanut butter. Viscosity is dictated by the ability of the molecules within the gel to move past one another, which relates to the size and molecular weight of the particles (Fig. 7).

The elastic modulus (G’) refers to the stiffness of a substance, which is its ability to resist deformation. For example, gum has a greater G’ than does pudding and if used to fill a space would be more resistant to deformation if an external force were applied. G’ is a function of bond strength, which determines the degree that the bonds can stretch when stressed. In other words, G’ reflects the ability of the bonds to resist expansion and contraction (Fig. 8). Clinically, a higher G’ translates into greater tissue lift.

A product with lower G’ and viscosity (e.g., Juvéderm; Allergan) is associated with a softer feel, greater spread, and less tissue lift. A higher G’ and viscosity (e.g., Restylane; Galderma) is associated with greater firmness, more limited spread, and greater tissue lift. A ranking of these properties for available HA agents is presented in Figure 9.
A greater degree of cross-linking of the HA gel correlates to a longer duration of effect, and the overall charge of the gel influences how hydrophilic it behaves. The number of HA products on the market reflects the ability to chemically engineer varying degrees of these parameters. Because of these factors, it is generally accepted that these products are not only distinguished by trade name but by important molecular properties that must be understood by the clinician using them.

**FDA-Approved HA Fillers**

Restylane was the first HA filler to receive FDA approval for use in the US (2003), for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. In 2010, the FDA approved Restylane-L which contains 0.3% lidocaine (Fig. 10). In June 2014, the FDA approved Restylane Silk (Fig. 11) for submucosal implantation for lip augmentation and for dermal implantation for the correction of perioral rhytides. Restylane Silk also contains 0.3% lidocaine. Restylane and Restylane-L are produced from bacterial fermentation of *S. equi* at a concentration of 20 mg/mL, with a uniform

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**Figure 8.** G’ is a function of bond strength, which determines the degree to which the bonds can stretch when stresses. G’ therefore reflects the ability of the bonds to resist expansion and contraction.

**Figure 9.** Viscosity rankings. A product with lower G’ and viscosity (e.g., Juvederm, Allergan) is associated with a softer feel, greater spread, and less tissue lift. A higher G’ and viscosity (e.g., Restylane, Galderma) is associated with greater firmness, more limited spread, and greater tissue lift.
particle size of 400 μm. Restylane is 1% cross-linked with epoxides, which is less cross-linking than that of other HA injectables yet the bond is more stable. The stabilized cross-linking is thought to contribute to prolonged efficacy by stimulating collagen synthesis and inhibiting collagen breakdown.132

In 2006, Matarasso et al.133 provided detailed consensus recommendations for Restylane use to optimize patient outcomes. Restylane has been directly compared with a number of other commercially available HA products. A detailed summary of those trials was presented by Rohrich et al. in 2011.112 Additional Restylane products have been designed for different depths with different size particles.133

Perlane (Galderma) is designed for deeper injection for coarser wrinkles. It was FDA approved in 2007 for the correction of moderate to severe facial folds and wrinkles. Similar to Restylane, Perlane has a higher G’ and viscosity and is therefore firmer than other HA products, has less spread, and provides greater tissue lift. Its efficacy and safety have been well established for injection into mid to deep dermis for correction of nasolabial folds,80,134−139 marionette lines and perioral wrinkles,134,140 tear trough deformities,141 and lipoatrophy.142 Results have been reported to last up to 7 months.135 In 2010, the FDA approved Perlane-L, which contains 0.3% lidocaine (Fig. 10).

Juvéderm Ultra and Ultra Plus (Allergan) has a higher concentration of HA, 24 mg/mL, when compared with Restylane, with more cross-linking in an attempt to increase longevity. It was approved by the FDA in 2006 for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. In 2010, the FDA approved Juvéderm Ultra XC and Ultra Plus XC, both containing 0.3% lidocaine. Juvéderm is produced from S. equi bacterial fermentation. The particles are non-uniformly shaped for a smoother gel consistency. The Ultra and Ultra Plus formulations are made with variable cross-linking and particle sizes, with effects reported to last up to 12 months.13 These formulations are recommended for the treatment of the perioral and nasal areas.

Juvéderm Voluma XC (with 0.3% lidocaine), approved in 2013, was developed to address facial volume loss, and it is the first HA filler to be FDA approved for injecting deep into the malar area for volume enhancement. It consists of a 20 mg/mL concentration of HA and is highly viscous. Its efficacy was established in European clinical trials published in 2009143 and was confirmed by a recent randomized clinical trial in the US144 and by non-randomized trials assessing its efficacy and durability.145,146 Voluma has been reported to last up to 24 months144,145,147 and has high rates of patient and physician satisfaction.146−148
The Volbella formulation is manufactured to be less hydrophilic, thereby reducing water uptake and swelling. This feature is desirable when injecting the lips. The product is available in Canada and is currently in clinical trials for FDA submission and approval. The addition of lidocaine (XC formulations) has been associated with less procedural pain (93% of patients).149,150

Prevelle Silk (Mentor Worldwide, LLC, Santa Barbara, CA) is indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Belotero Balance (Merz Aesthetics) (Fig. 12) was FDA approved in 2011 to correct moderate to severe facial wrinkles and folds, such as nasolabial folds. Belotero is derived from S. equi, and does not contain lidocaine. It is distinctive in that it uses varying degrees of cross-link density, a feature referred to as a polydensified matrix.78 The result of this is a prolonged duration of effect with preservation of a soft texture, allowing for more precise corrections of fine lines. The product consists of high- and low-molecular-weight polymers, with a mean size of 1196 kDa and 297 kDa, respectively.151 It has the highest mean molecular weight and greatest proportion of high-versus low-molecular-weight polymers when compared with Restylane and Juvéderm Ultra.151 Because of this molecular composition, the viscosity of the product is low, providing for easier injection and improved natural distribution. This is supported by histological examination that revealed Belotero Balance diffused evenly throughout the non-papillary dermis without clumping.152 This was in contrast to Restylane, which deposited in large pools exclusively in the reticular dermis, and to Juvéderm, which formed clumps throughout the reticular dermis. A recent study using high-resolution ultrasound to investigate filler distribution supports these findings.153

The safety and efficacy of Belotero Balance was established in a series of studies beginning in 2006. A detailed review of these articles was presented by Lorenc et al. in 2013.154 Longevity of Belotero Balance is most often 6 to 8 months but has been shown to last as long as 14 months.155-157 In a head-to-head prospective, rater-blind, randomized trial comparing Restylane with Belotero for the treatment of nasolabial folds, Belotero resulted in markedly greater improvement in subjective skin assessment scores and was preferred by patients.158 Downie et al.159 presented a series of 93 patients with Fitzpatrick skin types IV, V, and VI and concluded that Belotero Balance is safe for use in patients with those skin types.

Based on a 2013 roundtable discussion of the use of Belotero, it is recommended that Belotero be injected into the intradermal and superficial subdermal plane using a 13-mm sharp, 27-gauge needle, or 30-gauge needle.160 Lidocaine can be mixed with Belotero in a 10:1 or 10:3 lidocaine:Belotero ratio, although this use is off-label and adequate mixing should be achieved to ensure proper dilution.161,162 A series of videos demonstrating the recommended injection techniques of Belotero in various anatomic locations was presented by Lorenc et al.160

A number of new HA fillers are available outside the US, and although they might find a place in the US market, we recommend that they not be imported until their clinical efficacy and safety have been evaluated. In addition, it is strongly recommended that any facial injectable product be purchased directly from the manufacturing company or a designated outlet to ensure that they are manufactured under approved FDA conditions that adhere to strict quality control requirements.

**Figure 12.** Belotero Balance. (Image courtesy of Merz Aesthetics.)
Non-HA Fillers

Soft-tissue fillers referred to as non-HA fillers contain synthetic, biodegradable materials. Products in this group, including Radiesse and Radiesse Plus (Merz Aesthetics) and Sculptra Aesthetic (Galderma) contain synthetic material that stimulates endogenous tissue growth. The advantage of these products is that the duration of action is typically longer than with most HA fillers, in some cases reportedly up to 2 years. The disadvantage of a longer duration of action is that if results are not acceptable, the product has to be removed, which can be inherently difficult.

Poly-L-lactic Acid (PLLA)

PLLA is a biodegradable, nontoxic, synthetic, and inactive material derived from cornstarch in the alpha hydroxy acid family. It has been used in suture material, stents, and other biomedical implants.

Sculptra (Galderma) (Fig. 13), known as New-Fill in Europe, was FDA approved in 2004 for restoration and/or correction of the signs of lipoatrophy (facial fat loss) in people with or receiving treatment for human immunodeficiency virus. The lipoatrophy is thought to result from the use of highly active antiretroviral therapy. In 2009, Sculptra Aesthetic received FDA approval for the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate. Injection of 0.05 to 0.1 mL per square centimeter has been recommended by Schierle and Casas.

Sculptra consists of microspheres in a powdered form containing 150 mg of PLLA, 127.5 mg of non-pyrogenic mannitol, and 90 mg of sodium carboxymethylcellulose. Because of the hydrophobic nature of PLLA, the product requires reconstitution at least 3 hours before use, with some clinicians reporting up to 1 month of reconstitution with bacteriostatic water.

PLLA is metabolized to carbon dioxide, glucose, and water for several weeks after injection. This results in a delayed effect, often taking up to 2 months to reach the desired effect after initial injection, and it is recommended that patients be adequately counseled regarding this feature. Once the desired result is achieved, the clinical effect can be seen for 18 to 24 months. The long-term soft-tissue augmentation is caused by the stimulation of fibroblasts and growth of type I collagen into areas of accumulated PLLA microspheres. It is best used as a three-dimensional volumetric filler, as opposed to a superficial line filler. Sculptra often requires a series of injections to achieve adequate correction. Palm and Chayavichitsilp, Fitzgerald and Vleggaar, and Lorenc provided detailed reviews of injection techniques and recommendations for Sculptra use.

Calcium Hydroxylapatite (CaHA)

CaHA is found naturally in the body as the mineral component of bone and is highly biocompatible. It has been used in dental, orthopaedic, urological, and vocal cord applications. It acts as a biostimulatory scaffold for collagen ingrowth.
Radiesse (Fig. 14A) was approved by the FDA in 2006 to restore and/or correct the signs of lipoatrophy in people with the human immunodeficiency virus and for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Radiesse is composed of 24 to 45 μm CaHA spheres suspended in a 70% aqueous carboxymethylcellulose gel. It is highly viscous and predisposed to nodule formation, especially on the lips, a complication reported to occur in more than 20% of patients in some studies. \(^{161,177-179}\) Deep injection subdermally or intramuscularly is recommended. The gel matrix is absorbed in 6 to 8 weeks, and over time, the CaHA microspheres are metabolized while serving as a scaffold for collagen ingrowth. Longevity is generally 9 to 18 months, but the effects have been reported to last as long as 2 to 5 years. \(^{180-183}\) A multicenter, blinded, split-face, randomized clinical trial found Radiesse to be superior to Juvederm and Perlane for improvement in nasolabial fold depth. \(^{139}\) A similarly designed study by the same authors concluded superiority of Radiesse over Restylane. \(^{184}\) Radiesse can be safely combined with local anesthetic without loss of efficacy. \(^{185-187}\) Dallara et al. \(^{188}\) provided detailed consensus recommendations for the use of Radiesse. In January 2015, the FDA approved Radiesse Plus, which contains 0.3 mL of lidocaine (Fig. 14B)

**SPECIAL TOPIC: HAND REJUVENATION**

A topic of recent interest is the use of fillers for hand rejuvenation. Aging hands are characterized by dermal thinning and loss of subcutaneous fat, which leads to prominence of the musculoskeletal and venous structures of the hand. Injection of HA products into the subcutaneous tissue and mid dermis of the hand has been reported, with results lasting 6 to 9 months. \(^{189-191}\) The efficacy and safety of Sculptra for hand rejuvenation when injected into subcutaneous tissue has been published, with some studies finding sustained results at 15 months. \(^{192-195}\) Radiesse has become a popular option for hand rejuvenation and has been more extensively studied for this purpose.
compared with HA and Sculptra. Its safety and efficacy for volume restoration of the aging hand have been well established, with results lasting from 1 to 2 years. To receive hand rejuvenation fillers, patients are placed in the Trendelenburg position to reduce venous pressure. The injections proceed parallel to the metacarpals or in a fanning pattern. Massage of the area is recommended to prevent nodule formation, particularly with the use of Sculptra. Patients are asked to keep their hands elevated for 24 hours after the procedure to minimize edema, particularly with Radiesse. A randomized study to validate a hand grading scale was conducted (supported by Merz Aesthetics). The results of the live validation study showed consistent inter- and intrarater agreement. The hand grading scale is considered suitable for live assessment in clinical studies to grade dorsal hand conditions. After reviewing data presented in March 2015, the FA Advisory Panel recommended approval of Radiesse for hand rejuvenation. Approval is expected later in the year.

Permanent Injectables

Polymethylmethacrylate (PMMA)

PMMA, developed in 1928, is also known as Plexiglas, Acrylite, Lucite, and acrylic glass. It has been used in numerous medical applications for years, including bone cement, lenses, dental work, and pacemakers. Bellafill (formerly called Artefill; Suneva Medical, San Diego, CA) (Fig. 15) is a gel suspension of 20% PMMA homogeneous 30- to 42-μm microspheres in 3.5% bovine collagen solution mixed with 0.3% lidocaine. Because it contains bovine collagen, patients must undergo skin testing 1 month before injection. Bellafill received FDA approval for the correction of moderate to severe atrophic, distensible facial scars on the cheeks in patients older than 21 years.

Autologous Fat

Autologous fat is the original injectable. It is fully biocompatible and plentiful. Unfortunately, the degree of permanency varies. A technique has been described in detail by Coleman, and various techniques of harvesting, handling, and grafting have been attempted and have resulted in acceptable patient satisfaction. Successful fat grafting involves diffuse infiltration using multiple passes while grafting small aliquots of fat with each pass. This is thought to increase the contact area of the grafted fat with the recipient tissue vascular bed, improving long-term viability. The grafted fat seems to stabilize at approximately 4 months but can continue to lose volume for up to 1 year. Shuck et al. provided a review of safety, efficacy, and long-term outcomes of autologous fat grafting for human immunodeficiency virus-associated lipoatrophy.

Autologous Dermis

The use of autologous dermis as an injectable filler is currently under investigation. Bassetto et al. presented a series of 16 patients undergoing concomitant cosmetic procedures who were later injected with morselized autologous dermis for lip or nasolabial fold correction. Volume was maintained in all 16 patients at 1 year. Two patients experienced 6 months of palpable firmness over the injected area. This technique has not been studied extensively and is available only to patients who are undergoing concomitant Procedures requiring excision of dermis.
Silicone

Injectable silicone is produced from silica and polymerized dimethylsiloxane and is inert. It is FDA-approved for use in the eye for severe retinal detachment. A microdroplet (0.01–0.03 mL) injection technique allows for dispersion in tissue, where the material can become encapsulated as microparticles. The two brands available are Silikon 1000 (Alcon, Fort Worth, TX) and Adaptilosil 5000 (Bausch & Lomb, Rochester, NY). The numbers 1000 and 5000 correlate to the viscosity in centistokes (cSt), with water having a viscosity of 1 cSt at 20 degrees Celsius. The use of these products as injectable fillers for cosmetic purposes is off-label. Narins and Beer provided a review of the technical considerations, complications, and polarizing nature of injectable silicone. Fulton and Caperton presented a series of 95 patients who underwent injection with Silikon emulsified in cross-linked HA and concluded that the combination is safe, effective, and permanent.

Its use in Europe has been extensively studied, with the results of more than 15,000 patients represented in clinical trials and data indicating a duration of effect lasting up to 15 years. High patient satisfaction is consistently reported along with low rates of adverse effects. A detailed review of injection techniques, indications, and applications of ArteFill can be found in a paired series by Lemperle et al. Considering that ArteFill is a permanent product, proper technique is critical to prevent complications such as ridge formation, nodules, and long-lasting erythema.

PATIENT SELECTION

Satisfaction is a priority considering that injectables for facial rejuvenation are elective cosmetic procedures. Proper patient counseling should include goals, limitations, complications, and the realistic financial commitment associated with injectables. Photographs assist in documenting and addressing areas to be treated.

Before placing injectables, a complete patient history should be obtained, including current medications and herbal supplements, previous allergic reactions and sensitivities, previous facial rejuvenation (procedures, implants, or injectables), and personal medical history, including acne, keloids, dental abscesses, herpes simplex infections, and immunocompromised states.

If possible, patients should discontinue medications, including herbal supplements (arnica, garlic, ginger, ginseng, 
Gingko biloba, St. John’s Wort, vitamin E, etc.), that might cause bleeding 7 to 10 days before procedures to decrease bruising. Patients who are taking aspirin, non-steroidal anti-inflammatory drugs, Coumadin (Bristol-Myers Squibb, Washington, DC), or Plavix (Bristol-Myers Squibb; and Sanofi US, Bridgewater, NJ) might have medical indications for which the risk of stopping these medications (≤50%) could far outweigh the benefit. The guidelines put forth by the American College of Chest Physicians recommend continuance of anticoagulation for minor dermatological procedures with low risk of bleeding.

INJECTION TECHNIQUES

It is important to realize that practitioners are performing procedures that implant foreign materials. Contamination should be avoided to reduce infectious adverse events. Hands should be washed. Make-up should be removed and reapplication delayed at least 4 hours. Skin should be cleansed before injection. A sterile technique should be used during reconstitution and dilution of product. One should consider changing gloves after intra-oral manipulation. Injection during active skin infections should be avoided. Use of the smallest needles to achieve the desired effect is recommended.

The importance of skin preparation with injectables is unknown. Alcohol cleansing is commonly performed. Alternatively, Betadine can be used. Calfee and Farr found no difference in contamination of blood cultures between 10% iodine, 70% alcohol, or a combination of the two, concluding that alcohol be used considering cost. Chlorhexidine might have the benefit of a residual
antibacterial effect not achieved with alcohol and is currently recommended for use before placement of central venous catheters. Of note, chlorhexidine should be avoided in the periorbital region because of the associated risk for keratitis. It is important to remember to spread the skin during cleansing to get into wrinkles. Prophylactic antibiotics have been suggested to prevent biofilms in situations in which semi-permanent or permanent fillers are used initially or later during notable infections.

Topical anesthetics or nerve blocks can be used; however, concomitant injection of local anesthetic and fillers has been described and is gaining popularity. Needle gauge and length vary depending on the product, dilution, and application location. Smaller needles might reduce pain, injection site trauma, adjacent tissue trauma, and risk of infection. As a general rule, the smallest needle that allows accurate injection with optimal results should be used: 30-gauge for less viscous, 27-gauge for more viscous, such as CaHA, or 25-gauge for poly-L-lactic acid to avoid clumping or clogging. Lemperle et al. recommended using a 26-gauge needle, which acts as a guide to dermal thickness. The outer diameter of the needle is 0.5 mm, whereas the dermis is two needle diameters in thickness: 1 mm in frown lines (facial dermis range, 0.4−1.2 mm). General visual clues regarding needle depth include the following: intradermal, see the gray of the needle; superficial subdermal, see the shape of the needle; and deep subdermal, fat is pressed down with the tip of the needle. Arlette and Trotter reported that despite classic teachings of dermal injection, the majority of product is found in the subcutis. Several injection techniques are commonly described (Fig. 16).

The serial puncture and droplet technique deposits small aliquots by using multiple injections along the wrinkle or fold. Injections are placed close together to allow the filler to blend into a smooth, continuous line that lifts the wrinkle or fold, which can be assisted by molding and massage. The technique is useful for enhancement of the philtral columns and for correction of fine rhytides.

Linear threading deposits the injectable as the needle is advanced (anterograde) or withdrawn (retrograde). Anterograde injection might be less painful; theoretically, it minimizes trauma by hydrodissection and might cause less bruising by pushing blood vessels out of the way. This technique might be useful for enhancing the nasolabial folds and the vermilionocutaneous border by finding the potential spaces with limited needle movement. Retrograde injection might avoid intravascular injection, as in the glabellar region, and does not create additional tracks or dissection planes.

Fanning involves multiple passes in different directions without withdrawing the needle. The needle can also be passed several times, superimposing deep and superficial layers of fillers, which is thought to achieve superior results for the nasolabial fold.

Cross-hatching involves linear injection in an evenly spaced grid pattern. This is effective for large areas, three-dimensional filling, and the oral commissures.

Glogau and Kane conducted a prospective, blinded, controlled study of injection techniques. They found that techniques that increase the dissection of the subepidermal plane (fanlike needle use, rapid injection, rapid flow rates, and higher volumes) increase the incidence of local adverse events whereas injection techniques that increase epidermal damage (multiple punctures, deep subcutaneous injection) have no effect on adverse events.

A recent enhancement to injection of soft-tissue fillers is the use of a blunt-tip cannula. Because of the nature of a blunt tip versus a sharp needle, these devices produce less trauma to the tissues and decrease the risk for blood vessel rupture. The result is less bruising and less pain. In addition, the use of blunt-tip cannulae allows the physician to treat larger areas with fewer injection points. Blunt-tip cannulae are available in many sizes from a variety of companies.

Post-procedure management can include cold compresses or ice to help reduce swelling and tenderness. Reduced facial expression for the first 48 hours might minimize migration.
COMBINATION THERAPY

With the evolution of the understanding of facial rejuvenation, combination modalities are increasing to address the three-dimensional face. Stacking of fillers, especially permanent on top of permanent, and large-volume injections have been associated with more inflammation and granuloma formation. Carruthers and Carruthers conducted a prospective, randomized study of Botox in combination with HA filler and observed improved outcomes in comparison with those of HA filler alone for glabellar rhytides. The combination treatment almost doubled the duration of response. Carruthers et al. published their consensus recommendations for botulinum toxin and HA combination therapies in 2008.

COMPLICATIONS

Injectables available in the US have excellent safety profiles with rare side effects. The most common complications are procedural or technique-related as opposed to product-based, such as inappropriate placement of injectables, usually too superficially. Adverse reactions to injectables generally are transient and mild and include redness, swelling, bruising, and itching. Early injection site reactions can be limited by applying ice or cold compresses to minimize bruising and swelling.

Nodule formation is a complication that can occur with all fillers but is particularly common.
with Sculptra and Radiesse because of their molecular characteristics. A nodule formation rate of up to 52% has been reported for Sculptra, however, a low nodule rate of 4.2% was published in a study by Schierle and Casas. The authors attribute the low rate to their reconstitution technique.

Hypersensitivity to fillers can be as severe as angioedema and anaphylaxis. Antihistamines, topical immunomodulators (Aldara; Graceway Pharmaceuticals, LLC, Bristol, TN), tacrolimus, and steroid injections are effective in managing immunological reactions.

Injections around the lips can trigger herpetic outbreaks. If the patient has a history of herpes, prophylactic antiviral treatment should be considered, especially when injecting around the lips.

Intra-arterial injection can cause injection site necrosis and has been reported to occur in both the supraorbital artery during glabellar injection and the angular artery during injection of the nasolabial folds. The glabella is thought to be at highest risk because the supratrochlear artery provides a watershed area. It is always important to remember the anatomy when using injectables. Specifically, the supratrochlear artery runs deep (therefore, injections should be superficial) whereas the angular artery runs superficially (thus, injections should be deep). Venous occlusion can also occur if excessive product placement results in venous external compression. This might present as dull aching pain and swelling with violaceous discoloration.

Vascular embarrassment can be minimized by simple techniques. Always aspirate before injection. Use lower volumes in high-risk areas. Remember knowledge of vascular anatomy and depth planes. Treat one side at a time. Pinch or tent the skin to provide more space. Occlude the vessels at their origins.

Early intervention when encountering vascular compromise might prevent necrosis, with the goal of increasing blood flow. The procedure should immediately be aborted and the area massaged to disperse the material. Warm gauze and nitroglycerin paste will promote vasodilation. Hyaluronidase injection (for HA fillers) can be used to decompress the vessels. Hyperbaric oxygen can be considered.

The Tyndall effect refers to the blue discoloration seen when soft-tissue fillers are injected too superficially. This occurs because of light scattering differently depending on the diameter of particles encountered. Visible blanching and immediate appearance of lumps and bumps are technical errors of product placement, such as filler placement that is too superficial, which can be avoided by slowing down the injection and using finer-gauge needles. This will avoid inflammatory nodules or hypertrophic scarring. Although Belotero has been reported to not cause a Tyndall effect, even with superficial injections, care should be taken when injecting fine rhytides. Immediate massage of products might minimize nodules or irregularities.

Late complications include migration, discoloration, scarring, atrophy, biofilm development, and foreign body granulomas, which is the body’s attempt to remove unfamiliar material. Foreign body granulomas occur at an incidence of 0.01% to 0.1% for most fillers. Histologically, the granulomas consist of inflammatory lymphocytes, neutrophils, eosinophils, multinucleated giant cells, and plasma cells. Causes of granuloma formation include using high-viscosity fillers, large-particle fillers, impure products, and biofilms. The diagnosis of filler foreign body granuloma should be based on clinical findings. Steroid injections are proven treatments of granulomas. Cassuto and Sundaram provided an overview of the classification and recommendations for treatment of nodular complications after HA and CaHA filler injections.

Complications should be approached in an algorithmic manner, and early recognition is
important (Fig. 17). If the injection was performed by someone else, every attempt should be made to determine what was injected into the site. A recent study argued for the use of infrared spectroscopy as an imaging modality to identify the specific filler injected into tissue in cases of severe adverse reactions. In cases with even very mild signs of infection, one should assume infection is present and prove it is not.

If the wound is fluctuant, it should be needle-drained and cultured. Cultures should be sent to the laboratory immediately for appropriate handling. Preliminary antibiotic regimens should consist of at least a two-drug therapy, such as administration of a quinolone and third-generation macrolide, to prevent further biofilm deposition. Macrolides have been shown to be uniquely effective, which seems to be related to improved accumulation in the subcutaneous fat (where the filler material typically resides), and they might also block quorum sensing. After a trial of antibiotics, intralesional high-dose steroids should be considered. If HA was used, hyaluronidase should also be considered. The use of laser-assisted evacuation of filler material as an intermediate step between medications and surgery can be considered. Excision should be the last step.

**ETHICS**

The majority of cosmetic injectable use is off-label, and it is illegal to commercially advertise any non-approved or off-label use. Off-label use must not be experimental and should have general acceptance by the medical community in peer-approved publications or presentations. The patient must be informed of the off-label use.

Three models for delivery of injectables by qualified providers are available: physician delivery model, physician extender delivery model, and combined delivery model. The individual physician of record is ultimately responsible to ensure that any non-physician administering injectables possesses the proper education and training. The American Society of Plastic Surgeons (ASPS) and the ASAPS published the *Joint ASPS & ASAPS Guiding Principles: Supervision of Non-Physician Personnel in Medical Spas and Physician Offices*. This publication provides guiding principles to protect patients and improve quality of care. A central registry, or filler passport, has been suggested to maintain records while also minimizing unqualified practitioners and unregulated products.

![Figure 17](image_url) **Figure 17.** Management algorithm of late and delayed complications of soft-tissue injectables (Reprinted with permission from Rohrich et al.)
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