Cosmetic Injectables:
Emerging Uses, Techniques, and Data

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Statement of Need

Office-based surgical procedures are safe and cost-effective, according to a recent review, increasing their appeal to a broad range of patients. With the aging Baby Boom generation seeking out these procedures, demand will continue to grow. According to the American Society for Aesthetic Plastic Surgery (ASAPS), Americans spent around $10 billion on cosmetic procedures in 2010 and again in 2011. In 2010, approximately 62 percent of that expenditure was on surgical procedures, 16 percent was on injectables, 16 percent was on skin rejuvenation, and 4 percent was on other treatment options. In 2011, $17.2 billion was spent on injectable procedures; $1.6 billion was spent on skin rejuvenation procedures; and over $360 million was spent on other non-surgical procedures, including laser hair removal and laser treatment of leg veins. It is essential that physicians be prepared to provide superior outcomes to meet this significant demand. Assessing outcomes of aesthetic procedures is important because patient satisfaction is the predominant factor in determining success. Improvement in patients’ quality of life is another important but under-studied factor. There have been many developments in the field of cosmetic surgery in the past few years. Nonetheless, clinicians face challenges achieving patient satisfaction. A recent systematic review in cosmetic procedures proposed that measurement of patient satisfaction must be procedure-specific, formally developed, reliable, valid, and responsive and should determine multiple domains of satisfaction. This review identified that current ad hoc and generic tools of evaluation are inadequate. Most patient dissatisfaction in aesthetic surgery is based on failures of communication and patient selection criteria, not on technical faults. Therefore, appropriate patient selection and effective communication are also important. In addition to these criteria, there is an increasing emphasis on evidence-based medicine in cosmetic surgery. In the field of cosmetic surgery, it is difficult for algorithms to determine the type of aesthetic procedure. However, evidence-based medicine and clinical trials in cosmetic surgery have the potential to provide high-grade practice recommendations in the future, which could give scientifically proven and effective treatment for patients. This prompts for the discussion of such concepts with practicing aesthetic surgeons.

Non-surgical facial aesthetics and rejuvenation are evolving rapidly due to changes in products, procedures, and patient demographics. These procedures are now the most commonly performed aesthetic treatments. From 1997 to 2011, there was almost a 200 percent increase in the total number of minimally invasive procedures, such as injectable, skin resurfacing, and laser procedures. Clinicians can benefit from ongoing guidance on products, tailoring treatments to individual patients, treating multiple anatomic areas, using combinations of products, and techniques to optimize outcomes. According to a report in Plastic Reconstructive Surgery, a multidisciplinary group of aesthetic treatment experts convened to review the properties and uses of botulinum toxin type A and hyaluronic acid fillers and to update consensus recommendations for facial rejuvenation using these two types of products. The group considered paradigm shifts in facial aesthetics; optimal techniques for using botulinum toxin A and hyaluronic acid fillers alone and in combination; the influence of patient sex, ethnicity, cultural ideals, and skin color; general techniques; patient education and counseling; and emerging trends and needs in facial rejuvenation. The group provided specific recommendations for facial area, focusing on relaxing musculature, restoring volume, and re-contouring using botulinum toxin type A and hyaluronic acid fillers alone and in combination. These experts concluded that optimal outcomes in facial aesthetics require in-depth knowledge of facial aging anatomy. An appreciation that rejuvenation is a 3D process involving muscle control, volume restoration, and re-contouring, and thorough knowledge of properties and techniques specific to each product in the armamentarium. In addition, patient satisfaction plays a pivotal role in the success of aesthetic procedures such as botulinum toxin treatment. The duration of effect is an important measure that influences the factors such as retreatment intervals, costs, and convenience to the patients. Using such advanced measures of satisfaction, a Canadian study recently identified two more effective injection regions in addition to the conventional site. CME activities are crucial so that expert physicians can share this type of information with practitioners.

Botulinum neurotoxin treatment is the most common aesthetic procedure in the United States, and has been since 2000. It is the most popular non-surgical procedure among men and among women. A number of serotypes and formulations are available worldwide, and the last three years have seen the approval of two new formulations on the US market. Clinicians desire education on the differences between formulations, and the FDA has imposed strict guidance on dosage discussions, as the agents are not interchangeable. A review revealed that injection patterns, techniques, dilutions, diffusion, and injection volumes established for a specific formulation of botulinum neurotoxin are not likely to be applicable to other formulations, and formulations are not interchangeable by any single conversion ratio. Furthermore, the duration of effect as well as the proportion of patients relapsing after 16 weeks seems to vary among specific formulations. Therefore, it is important that practitioners are aware of the specific properties and techniques associated with each product. In April 2009, FDA issued warnings and a labeling updates for all botulinum toxins. The agency cautioned that the effects of agents may spread beyond the injection site, producing unintended paralytic and/or symptoms of botulinum poisoning.
The following underlying educational needs should be addressed to bridge the gap between existing and ideal knowledge in today’s cosmetic surgery milieu.

- Increased understanding of the available botulinum toxin agents and their safety considerations
- Improved appreciation of the use of injectable fillers, their associated treatment regimens, and the management of adverse events
- Improved ability of patient selection and to manage complications
- Strategies to improve communication between patients and physicians regarding patient expectations, postoperative outcome, and patient satisfaction.

If these learning needs are properly met, more patients will benefit from clinical advancements that can improve treatment outcomes and quality of living. Health care authorities increasingly call for dermatologists and other physicians to follow evidence-based recommendations to maximize treatment efficiency, increase effectiveness of care, and to ensure optimal patient outcomes. In order to achieve these goals, dermatologists need to arm themselves with the most current knowledge, which were discussed in the previous section, to effectively monitor treatment effectiveness and alter treatment plans when necessary.

Like other medical professionals, dermatologists routinely turn to expert colleagues for knowledge that will help them develop the most effective patient management and therapeutic strategies. This proposed CME activity will provide evidence-based information from experts addressing the critical decisions required of practicing dermatologists during cosmetic surgery procedures. The activity will also provide perspectives to help clinicians plan for near-term future therapeutic developments in this clinical area.

Dissemination of information by experts experienced in clinical research and patient care is critical to address practicing dermatologists’ underlying educational needs, allowing them to confidently overcome demonstrated practice gaps. In the field of cosmetic procedures, patient satisfaction, low risk-benefit ratio, and patient’s quality of life are the primary success goals to be achieved by the physicians. Addressing patient management and therapeutic options for cosmetic surgery can provide education that is immediately applicable to clinical practice.

20. 2011 AMPPRS Membership Study
22. American Academy of Dermatology Association. AARD.org

**Target Audience**

This certified CME activity is designed for dermatologists and dermatology residents.

**Learning Objectives**

- Upon completion of this activity, the participant should be able to:
  - Identify various uses of injectable fillers, their associated treatment regimens, and manage adverse events
  - Know the current developments in the field of cosmetic surgery and implement them in practice
  - Apply strategies to improve management of complications and proper patient selection to avoid dissatisfaction
  - Effectively educate patients about known risks associated with cosmetic therapies
  - Establish protocols in their practices to monitor and disseminate accurate information about emerging therapeutic concerns
  - Formulate and implement advanced patient satisfaction evaluation methods
  - Utilize cosmetic treatment procedures that result in patient satisfaction, low risk-benefit ratio, and improved quality of life for patients

**Accreditation and Designation**

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and Practical Dermatology. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Method of Instruction**

After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit http://www.dulaneyfoundation.org and click “Online Courses.” Upon completing the activity and achieving a passing score of over 70 percent on the self-assessment test, you may print out a CME credit letter awarding 1 AMA PRA Category 1 Credit™. The estimated time to complete this activity is 1 hour.

**Disclosure**

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and US Food and Drug Administration guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity participants (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/ devices or providers of commercial services and (2) identification of a commercial product/ device that is unlabeled for use or an investigational use of a product/device not yet approved.

**Faculty Credentials**

Macrene Alexiades-Armenakas, MD, PhD, FAAD is Assistant Clinical Professor at Yale University School of Medicine, New Haven, CT. She is founder and Director at NY Derm LLC in New York, NY.

David E. Bank, MD, FAAD is Director, The Center for Dermatology, Cosmetic & Laser Surgery in Mt Kisco, NY.

Vic A. Narurkar MD, FAAD is the cofounder of Cosmetic Boot Camp LLC and founder of the Bay Area Laser Institute in San Francisco. He serves on the board of directors of the AAD and is the chair of dermatology at California Pacific Medical Center, San Francisco, CA.

Susan H. Weinkle, MD, FAAD is board-certified in dermatology. She is a Fellow of the American College of Mohs Surgery and Cutaneous Oncology and a Diplomat of the American Board of Dermatology. She is in private practice in Bradenton, FL.

**Faculty/Staff Disclosure Declarations**

Dr. Alexiades-Armenakas has disclosed no relevant conflicts of interest.

Dr. Bank has disclosed the following relevant financial relationships: Allergan, Inc. and Medicis Pharmaceutical Corporation.

Dr. Narurkar has disclosed the following relevant financial relationships: Allergan, Inc.; Merz, Pharmaceuticals, LLC; Myoscience; Palomar Medical Technologies, Inc.; Philips Healthcare and ZELTIQ Aesthetics, Inc.

Dr. Weinkle has disclosed the following relevant financial relationships: Allergan, Inc.; DermAdvantage; Ethicon, Inc.; Galderma Laboratories, LP; Xthera; Medicis Pharmaceutical Corporation; Myoscience; Procter & Gamble Pharmaceuticals; TEOXANE Laboratories; and Valeant Pharmaceuticals International.

All of those involved in the planning, editing, and peer review of this educational activity report no relevant financial relationships.
Dermatologic surgeons performed nearly one million cosmetic soft tissue filler injections last year, according to results of a recent ASDS membership survey. These procedures are clearly popular and continue to grow (Fig. 1), as has the number of available fillers on the US market (Table 1). The number of fillers available internationally is even greater. Dermatologists weighing the various filler agents currently on the US market and those that are forthcoming face the daunting task of assessing studies that vary significantly in their design and endpoints.

Wrinkle fillers are cosmetic devices regulated by the FDA and brought to market under the Premarket Approval (PMA) process. The fillers currently available on the US market vary in terms of their indications, intended depth of placement, their biologic activity, and their duration of effect (Table 1). Hyaluronic acid based products are primarily space filling. Calcium hydroxyapatite (CaHA) has a combined space filling and biostimulatory effect. Biostimulatory fillers, such as Poly-L-lactic acid (PLLA) or calcium hydroxylapatite (CaHA), initiate neocollagenesis to provide a volumizing effect over time. The duration of these “non-permanent” fillers ranges from six months to two years. Finally, among the “permanent” fillers are silicone and Polymethyl methacrylate (PMMA), which is also a stimulatory filler. The biologically inert microspheres serve as a scaffold for collagen rebuilding.

The regulatory requirements for filler approval differ from those for drug approvals. In comparison to typically much larger drug approval studies, many of the filler agents were cleared for marketing based on studies involving approximately 150 to 200 treated subjects under the PMA approval process which, according to FDA, “is the required process of scientific review to ensure the safety and effectiveness of Class III devices.” Thus, these smaller study populations may not yield the quantity of data that physicians are accustomed to seeing for drugs and leave injectors with additional learning through experience.

Like approved drugs, PMA devices are authorized with specific indications. Among the fillers to have received PMA clearance, there is some variability in the language of approved uses. For example, while the PMA approval letters for some agents discuss injection into “facial tissue,” others have more specific labeling: most of the hyaluronic acid fillers are approved for “injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds),” an indication that is inconsistent with current practice patterns.

Like approved drugs, approved devices can be used “off-label,” and most clinical practice patterns would qualify as such. In fact, for the treatment of nasolabial folds (NLFs), injection of hyaluronic acid into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds),” an indication that is inconsistent with current practice patterns.
A recent study histologically assessed average dermal thickness, as well as the depth of placement of hyaluronic acid (HA) fillers in a cohort of 16 patients who were to undergo tissue excision for Mohs microsurgery. The analysis found that the thickness of the dermis in the NLFs was just 1.37±0.27 mm (mean±SD)—a challenging target for placement of fillers. In fact, for all 16 patients assessed in this study, HA filler placement was localized to the subcutis. In nine of 16 tissue samples, some HA was present in the deep dermis, but only one patient had filler in the superficial dermis. The thickness of injected filler was 2.11±0.63 mm, but filler was often transected at the specimen base.

A separate ultrasound study confirmed that superficial placement of HA filler in the superficial dermis (0.2mm) is possible, but it is associated with adverse events, especially clinical erythema and tenderness, and an eosinophilic infiltrate was associated with biphasic gels histologically. Injection of HA fillers into the dermis, as indicated by the FDA, could lead to the formation of bluish discoloration (Tyndall effect), nodularity, and bleeding at significant rates. For these reasons, the common terminology of “dermal” fillers should be abandoned.

Referring to these devices as cosmetic “fillers” may not fully reflect the potential activity of these agents (Fig. 2). Evidence now shows that, in addition to “filling” lines and wrinkles, HA injections can induce persistent neocollagenesis, a concept further explored below. Furthermore, these agents increasingly are used for lifting and global volumizing effects, rather than correction of individual wrinkles.

Among injectable cosmetic devices, HA-based formulations are far more popular than the other classes of fillers, due in significant part to their reversibility, versatility, and safety. As such, they will be the focus of the remainder of this paper.

**MANUFACTURE OF INJECTABLE HA FORMULATIONS**

The relative safety of HA fillers, when properly administered, is well established. Although there are recognized and potentially significant adverse events (AEs; which may be associated with product placement and injection technique, as discussed below) associated with these agents, their incidence tends to be rare. The efficacy of these agents is also well established. A recent analysis of 53 primary clinical reports for HAs determined that the highest evidence was available for their use in the NLFs, which was evaluated in 10 randomized, blind, split-face, comparative trials. Several randomized, blind trials support treatment of the glabella, lips, and hands, but the evidence for the nasojugal folds (tear troughs), upper eyelids, nose, infraorbital hollows, oral commissures, marionette lines, perioral rhytides, temples, and cheeks is lower-level (from studies with non-randomized, open-label, or retrospective designs). In this review, common AEs across anatomic areas were pain, bruising, swelling, and redness. Serious AEs were uncommon (eight events in eight of 4,605 total patients) and probably not related to treatment.

The available HA agents differ in their characteristics, owing in large part to differences in their manufacture and formulation. Hyaluronic acid is a naturally occurring polysaccharide formed by repeating D-glucuronic acid and DN-acetylglucosamine disaccharide units. It occurs naturally in the human body, including in the skin. Its hydroscopic properties make HA a suitable volumizing agent. It has a low potential to induce adverse reactions.

Hyaluronic acid is supplied to manufacturers as a white powder that is dissolved in water to create a viscous clear liquid, which is known as free HA. Unmodified, non-cross-
linked HA has a half-life in the skin of about 12 hours. If injected in the skin, free HA would be quickly absorbed by the body after enzymatic degradation via endogenous hyaluronidase and reaction with reactive oxygen species, such as superoxide and peroxynitrite. Therefore, free HA has no persistent effect as a filling agent. In order to provide a persistent filling effect, HA must be cross-linked through the use of chemical cross-linkers. Approved chemicals for use in the US are 1,4-butanediol diglycidal ether (BDDE) and di-vinyl sulfone (DVS), BDDE being the one currently in use in marketed HA fillers. High-level BDDE exposure is associated with the development of liposarcoma, leading the FDA to stipulate limits on the total amount of residual free BDDE in a formulation.

Crosslinking binds HA polymer chains together to produce polymer networks, resulting in the formation of an HA gel. As the degree of crosslinking increases, so does the firmness of the resulting gel. This raw gel is not itself suitable for injection, as the process of gel formation does not control for HA particle size; particles that are too large will not be readily extruded through a needle into the skin. To create HA molecules of sufficiently small size, the gel may be sieved. The resulting consistent small size particles are then suspended in free HA, forming a granular biphasic gel for injection into the skin. The free HA serves as a lubricious base for the formulation, facilitating injection and perhaps providing a short-term hydrating effect, but it quickly dissipates and offers no lasting volumizing effect.

Alternatively, homogenization of the raw gel can be performed to create a white, monophasic gel with a smooth consistency. The actual HA particles within this smooth gel may be of different sizes, but all are small enough to be extruded through a needle. These irregularly shaped particles may be more closely packed than spherical particles and are able to interlock, creating a continuous gel.

Because multiple smaller molecules present a larger surface area for binding of enzymes and exposure to free radicals, relative to a larger molecule, one might predict that a small molecule HA will be more quickly degraded and therefore provide a shorter duration of effect. However, it appears that the porous nature of the HA molecule provides ample access to enzymes and free radicals, regardless of the HA particle size, to practically negate the influence of surface area.

Degree of crosslinking appears to influence in vitro durability of a formulation. The degree of crosslinking indicates the percentage of HA disaccharide monomer units that are bound to a cross-linker molecule (so that a filler with a degree of crosslinking of 4% has, on average, four crosslinker molecules for every 100 disaccharide monomeric units of HA). A higher degree of crosslinking will also tend to produce a harder gel.

Chemical properties of the formulations and aspects of their manufacture may contribute to unique physical properties, which have received a great deal of attention, despite their sometimes unclear clinical significance.

RHEOLOGICAL PROPERTIES

“Rheology” or “the study of the deformation and flow of matter” has become a prominent topic in discussion of cosmetic fillers, despite a significant degree of confusion about terms as well as the clinical relevance of rheological characteristics of individual formulations. Thus, a discussion of rheology is relevant, both generally as well as in the available published literature on injectable cosmetic devices specifically.

Viscosity or “resistance to flow” is a measure of shear force. In simple assays, viscosity is measured by placement of a liquid or semi-liquid material between two flat plates of glass. The shear rate is the force per unit area needed to move the top plate over the bottom. G’ or G-prime quantifies the deformation energy stored by the sample during the shear process. It is, therefore, a measure of elasticity or hardness. (In contrast, G” or G-double prime is a measure of the deformation energy used by the sample during the shear process.)

Cohesivity is a measure of a substance’s resistance to deformation. In the glass plate test, it is measured by pressing the top plate down upon a sample and measuring resistance force.

These technical, physical terms correlate with less precise but more clinically compelling concepts, such as flow, elasticity, and firmness. Attempts are made to correlate these properties with features of a formulation, such as particulate vs particulate formulation, consistency, degree of crosslinking, and even HA concentration.
<table>
<thead>
<tr>
<th>Filler Type</th>
<th>Trade Name</th>
<th>Material</th>
<th>Decision Date</th>
<th>Indication per PMA Approval Letter</th>
<th>Duration (per patient information)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primarily Space Filling</td>
<td>RESTYLANE-L INJECTABLE GEL (Medicis)</td>
<td>Hyaluronic Acid 20mg/mL with Lidocaine Biphasic</td>
<td>8/30/2012</td>
<td>Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles/folds (such as nasolabial folds) and for lip augmentation in those over the age of 21 years.</td>
<td>6 mos.</td>
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<td></td>
<td>BELOTERO BALANCE (Merz Pharmaceuticals)</td>
<td>Hyaluronic Acid 22.5mg/mL Monophasic/Cohesive</td>
<td>11/14/2011</td>
<td>Injection into facial tissue to smooth wrinkles and folds, especially around the nose and mouth (nasolabial folds).</td>
<td>6 mos.</td>
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<tr>
<td></td>
<td>RESTYLANE INJECTABLE GEL (Medicis)</td>
<td>Hyaluronic Acid 20mg/mL Biphasic</td>
<td>10/11/2011</td>
<td>Lip augmentation in those over the age of 21 years.</td>
<td>6 mos.</td>
</tr>
<tr>
<td></td>
<td>JUVEDERM ULTRA XC, JUVEDERM ULTRA PLUS XC (Allergan)</td>
<td>Hyaluronic Acid 22-26mg/mL 0.3% Lidocaine Monophasic/Cohesive</td>
<td>1/7/2010</td>
<td>Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).</td>
<td>9-12 mos.</td>
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<td></td>
<td>PREVELLE SILK (Mentor/Genzyme)</td>
<td>Hyaluronic Acid with Lidocaine</td>
<td>2/26/2008</td>
<td>Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).</td>
<td>n/a</td>
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<td></td>
<td>PERLANE (Medicis)</td>
<td>Hyaluronic Acid 20mg/mL Biphasic</td>
<td>5/2/2007</td>
<td>For implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.</td>
<td>6 mos.</td>
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<td></td>
<td>ELEVNESS (Anika Therapeutics) NOT CURRENTLY ON THE US MARKET</td>
<td>Hyaluronic Acid with Lidocaine</td>
<td>12/20/2006</td>
<td>Use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).</td>
<td>12 mos.</td>
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<td></td>
<td>JUVEDERM 30, 24HV, 30HV (Allergan, Inc)</td>
<td>Hyaluronic Acid 22-26mg/mL</td>
<td>6/2/2006</td>
<td>Use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).</td>
<td>9-12 mos.</td>
</tr>
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<td></td>
<td>RESTYLANE INJECTABLE GEL (Medicis)</td>
<td>Hyaluronic Acid 20mg/mL Biphasic</td>
<td>3/25/2005</td>
<td>Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).</td>
<td>6 mos.</td>
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<tr>
<td>Filler Type</td>
<td>Trade Name</td>
<td>Material</td>
<td>Decision Date</td>
<td>Indication per PMA Approval Letter</td>
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<tr>
<td>Primarily Space Filling (Continued)</td>
<td>CAPTIQUE INJECTABLE GEL</td>
<td>Hyaluronic Acid</td>
<td>11/12/2004</td>
<td>Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).</td>
<td>n/a</td>
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<td>NO LONGER ON THE US MARKET</td>
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<td>HYLAFORM (HYLAN B GEL)</td>
<td>Modified Hyaluronic Acid Derived from a Bird (Avian) Source</td>
<td>4/22/2004</td>
<td>Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).</td>
<td>n/a</td>
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<td></td>
<td>NO LONGER ON THE US MARKET</td>
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<td></td>
<td>RESTYLANE INJECTABLE GEL</td>
<td>Hyaluronic Acid Biphasic</td>
<td>12/12/2003</td>
<td>Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).</td>
<td>6 mos.</td>
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<tr>
<td></td>
<td>(Medicis)</td>
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<td></td>
<td>COSMODERM 1 HUMAN-BASED COLLAGEN</td>
<td>Collagen</td>
<td>3/11/2003</td>
<td>Injection into the superficial papillary dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars.</td>
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<tr>
<td></td>
<td>(Allergan, Inc)</td>
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<td></td>
<td>FIBREL</td>
<td>Collagen</td>
<td>2/26/1988</td>
<td>The correction of depressed cutaneous scars, which are distendable by manual stretching of the scar borders.</td>
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<td></td>
<td>ZYPLAST(R) (Allergan, Inc)</td>
<td>Collagen</td>
<td>6/24/1985</td>
<td>Use in mid to deep dermal tissues for correction of contour deficiencies.</td>
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<td></td>
<td>ZYDERM COLLAGEN IMPLANT (Allergan, Inc)</td>
<td>Collagen</td>
<td>9/18/1981</td>
<td>Use in the dermis for correction of contour deficiencies of soft tissue.</td>
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<td></td>
<td>EVOLENCE COLLAGEN FILLER</td>
<td>Collagen</td>
<td>6/27/2008</td>
<td>The correction of moderate to deep facial wrinkles and folds (such as nasolabial folds).</td>
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</table>
Products with high $G'$, such as the particulate HAs, tend to have low viscosity, requiring the incorporation of free HA, which is quickly degraded, in order to facilitate easier injections. These formulations tend to have lower cohesivity, as the cross-linked HA particles are suspended in the free-HA base. Greater crosslinking results in a softer, more cohesive, and more viscous formulation.

$G'$ is often described as a measure of gel hardness, though such characterization is somewhat oversimplified. It may be more precise to note that a harder gel will have a higher $G'$. Harder gels (and therefore gels with a higher $G'$) are associated with relatively greater lift capacity compared to softer gels. As the HA concentration increases, the $G'$ decreases. Similarly, as HA concentration and degree of crosslinking increase, maximum swell capacity decreases.\(^{12}\)

There has also emerged a faulty conception that higher $G'$ correlates to a more robust or more persistent filling effect. However, this is not necessarily accurate. Consider, for example, that collagen has a relatively high $G'$ value but is not particularly robust.

Rather than assume clinical characteristics of a given formulation based on its published $G'$ value, it is more practical and ultimately more responsible to assess each formulation’s distinct characteristics in light of the patient’s specific needs.

It should also be noted that clinicians may often modify marketed formulations for specific off-label clinical applications, changing their physical and chemical properties. Dilution or “reconstitution” is an increasingly common practice, described in the literature just last year.\(^{16}\) Dilution results in an injectable formulation with a reduced HA concentration that may be suitable for use to treat fine lines and tear troughs. It has also been suggested that dilution of HA with saline may result in a more even final distribution of HA, once the saline is absorbed by the body.\(^{17}\) There should be further study and consensus building around this off-label practice to establish standard dilution ranges for particular formulations and applications. Furthermore, clinicians should remain attentive to developments in the market, as new fillers, including some intended for superficial placement, are anticipated.

Physical modification of formulations is also possible. For example, using a 32-gauge rather than 27- or 30-gauge needle with Restylane will extrude a smaller diameter particle appropriate for fine lines.

**CLINICAL OUTCOMES**

There appears to be a consensus in the available literature that the biphasic HA gels, which have higher relative $G'$ values, have a higher lift capacity.\(^ {18}\) However, this assertion is disputed, as it has been suggested that the apparent lifting effect may be related to the attraction of water by the free HA in the biphasic formulations.\(^ {19}\)
There is evidence from Wang, et al. that injectable HA formulations stimulate neocollagenesis at the site of injection, perhaps accounting for the apparent increase in durability of results over time. Their study involved 11 healthy volunteers with photodamaged forearm skin who were injected with cross-linked HA dermal filler and isotonic sodium chloride (as control) into forearm skin. Skin biopsy specimens were taken at weeks 4 and 13. Immunostaining revealed increased collagen deposition around the filler in skin receiving cross-linked HA injections. Staining for prolyl-4-hydroxylase and the C-terminal and N-terminal epitopes of type I procollagen was enhanced at weeks 4 and 13 (P=.05). Gene expression for types I and III procollagen as well as several profibrotic growth factors was also up-regulated at these timepoints compared with controls (P=.05). Fibroblasts in filler-injected skin demonstrated a mechanically stretched appearance and a biosynthetic phenotype. In vitro, fibroblasts did not bind the filler, suggesting that cross-linked HA is not directly stimulatory.5 The authors of this study hypothesized that injection of cross-linked HA stimulates collagen synthesis, perhaps by mechanical stretching of the dermis and associated stretching and activation of dermal fibroblasts.

Further support for these properties was provided in a recent study involving patients injected with hyaluronic acid into skin of the buttocks, with biopsies taken at weeks 1, 2, 4, and 12.20 Researchers reported that age-related collagen fragmentation, fibroblast shrinkage, and reduced collagen production are largely reversed by enhancing the structural support of the dermal extracellular matrix (ECM). Injection of cross-linked HA stimulates collagen synthesis, perhaps by mechanical stretching of the dermis and associated stretching and activation of dermal fibroblasts.

Hyaluronic acids have different degrees of resistance to hyaluronidase, which may be a function of the degree of crosslinking and an indicator of long-term in vitro durability. In in vitro tests, after all dose responses and timed-interval tests, the 24-mg/mL HA smooth gel filler exhibited more resistance against in vitro enzymatic degradation to ovine testicular hyaluronidase than did the 20- and 5.5-mg/mL HA particulate gels. This resistance to degradation in vitro may be attributed to the higher HA content of the 24-mg/mL HA smooth gel, its high degree of crosslinking, and the cohesive property of the gel filler.21

A study using bovine hyaluronidase also found higher sensitivity to degradation for Restylane/Perlane than for Juvederm, associating the degree of sensitivity with degree of crosslinking and the monophasic or biphasic nature of the product.22 Each of the available HAs currently on the market was submitted to the FDA with evidence of persistence of effect for up to six months. Post-marketing studies suggest the duration may be longer, perhaps up to one year, for the monophasic HA gels.23 For one study, eligible subjects were randomly assigned to receive a single treatment with either Juvederm Ultra Plus or Perlane into the right NLF, with the alternative treatment administered into the left NLF.23 No “touch-ups” were permitted during the study. Physician investigators were not blinded to the product they were injecting, but the randomization code was kept secret from investigators at all timepoints following randomization. Subjects were blinded to treatment through the duration of the study.

Severity of each NLF was determined by the physician at baseline, days 3 and 7, and months 1, 3, 6, 9, and 12; study subjects were asked to assess the severity of each NLF at the same timepoints. By month 6, differences in the clinical performance favoring Juvederm were evident based on both physician and patient ratings (90 percent for Juvederm vs 65 percent for Perlane; P<0.0001 among physicians and 83.8 percent for Juvederm vs 72.5 percent for Perlane; P=0.06 among subjects). A statistically significant difference was evident at month 9. This differential effect in favor of Juvederm Ultra Plus was confirmed at the final clinical visit at month 12: 70.0 percent vs 45.0 percent; P=0.0002 among physicians and 62.5 percent vs 46.3 percent; P=0.01, among subjects).23

Both experience and published data suggest that repeat treatments with injectable HAs may lead to longer durations of effect and need for reduced volumes of agent to
achieve desired results. Subjects who received a repeat treatment at six to nine months post initial treatment needed 60 percent less filler at subsequent injections and sustained wrinkle correction for a total of 18 to 21 months. The authors acknowledge that the cause for the phenomenon is not clear. However, the data regarding neocollagenesis provides a possible explanation.

Anecdotally, it seems, experienced injectors are bound to encounter a patient who simply does not respond well to HAs or does not have a persistent improvement. Inadequate response may be attributed to improper depth of placement or to treatment of a patient who is not a true candidate for HAs and would be better served by a more invasive procedure. However, there are cases in which these factors do not seem operative. It has been hypothesized that these individuals may have high levels of engogenous hyaluronidase. Alternatively, there is interest in exploring the potential influence of HA antibodies, which has been studied minimally, though there appears to be little cause for concern. Just one publication reviews humoral and cellular immunogenicity of non-animal-stabilized hyaluronic acid (NASHA), based on data from prospective clinical trials involving NLF augmentation.

In two randomized clinical studies, 150 (10 centers) and 283 (17 centers) subjects receiving Restylane and/or Perlane had serum immunoglobulin (Ig)E and IgG anti-NASHA measured by immunoassay at weeks 0, 6, and 24 weeks and IgE anti-NASHA by intradermal skin testing (ID-ST) at weeks 0 and 24. All ID-STs and IgE anti-NASHA results were negative. Serologically, 91.8 percent of 425 subjects were negative for IgG anti-NASHA (<1.5 mg/mL) at all time points, whereas 7.8 percent had positive enrollment IgG anti-NASHA (range, 1.5–18.5 mg/mL) that remained essentially unchanged over the study period.

![Fig. 4. Post filler bruising (left) and following treatment with intense pulsed light source (right).](image-url)
THE TYNDALL EFFECT

The Tyndall effect, as it is widely known, is simply a matter of light-scattering. Certain molecules preferentially scatter certain lightwaves more than others. Just as molecules in the atmosphere preferentially scatter blue light, giving the sky its distinctive hue, hyaluronic acid placed superficially in the dermis will scatter and reflect blue light. Development of bluish discoloration—a Tyndall effect secondary to superficial placement of dermal fillers—has been acknowledged in the literature (Fig. 3). There are no comprehensive studies of the incidence of Tyndall effects across HA fillers or even for specific fillers, and none of the pivotal trials for HA fillers reports the incidence of bluish discoloration specifically.

One high-profile five-year retrospective study showed that in one clinic there was no evidence of any Tyndall effect among 317 patients (receiving 668 treatments) injected with Belotero, a finding that seems to support a popular supposition that this agent does not cause Tyndall effects. However, the reported injections were in the NLFs, where risk of Tyndall effects is already low. Furthermore, incidence of Tyndall side effects with other HA agents in the hands of these injectors is not known; the lack of Tyndall effects or any serious adverse events over five years may also be a function of the injectors’ expertise.

The Tyndall effect is a physical phenomenon. It is possible that the physical properties of a specific formulation may negate the potential for a Tyndall effect. In fact, in the experience of this panel, use of Belotero, including with relatively more superficial placement than is typically employed for other HAs, has not produced any Tyndall effect. However, there is insufficient evidence to make this claim at this time. A reasonable approach to patient care may be for injectors to assume that any agent may produce this undesired side effect and to favor those injection techniques that minimize the risk for AEs, regardless of the agent injected.

OTHER ADVERSE EFFECTS

Injection site reactions are the most common AEs associated with dermal fillers. These AEs, such as swelling or bruising, tend to be mild to moderate and to resolve within a few days. Lumpiness and bumps may develop if an agent is placed too superficially. Persistent nodules or granulomatous foreign-body reactions, have been reported but are rare.

A comprehensive review of the literature recently reported 32 cases of iatrogenic blindness reported in 29 articles. In nearly half the cases, blindness occurred after injections of adipose tissue; in the other 17, it followed injections of various materials, including corticosteroids, paraffin, silicone oil, bovine collagen, polymethylmethacrylate, hyaluronic acid, and calcium hydroxyapatite.

An emerging safety concern in the dermatology clinic is the inappropriate sourcing of injectable aesthetic agents and topical anesthetics. All injectable agents should be acquired only from distributors licensed by the respective product marketers in the US. Importation or re-importation of injectables from non-US-based distributors is illegal and puts patients at risk. Several professional physician groups within the US have condemned the practice.

Similarly, use of compounded injectables or topical anesthetics has also been associated with risks, including patient death, and should be avoided. The availability of FDA-approved agents obviates the need for compounding.

MINIMIZING AND MANAGING AEs

Avoidance of most AEs is possible with proper injection technique. In an analysis of the clinical trial data for NASHA small and NASHA large formulations, Glogau and Kane identified the following local AEs, the incidence of which was low and similar for each product: bruising (Fig. 4), tenderness, edema, and pain. Fanning injection technique, rapid injection, rapid flow rates, and higher volumes were all independently associated with higher incidence of adverse events.

Deep injection of fillers is advocated for many applications, including treatment of the temples and the malar pads, where material should be placed sub-muscularly above the periosteum and in the subcutaneous plane. Risk of developing emboli exists at any plane, but deep placement reduces the risk for nodules, granulomas, Tyndalling, and necrosis.

Arguably, the serial puncture technique may be associated with the lowest risk for AEs, as techniques such as fanning increase the risk for dissection of the subepidermal plane. Upon inserting the needle, the injector should pull back on the plunger to assure there is no blood (evidence...
of intravascular placement) and then inject a small aliquot before moving to the next injection site. However, the injection technique may have to vary based on the treatment population; serial puncture is not feasible in patients who may be at high risk for bleeding or bruising, such as those on anticoagulant therapy, for example.

Use of blunt-tipped cannulas has been advocated by some as a strategy to reduce risk of serious complications such as blindness, stroke, and skin necrosis that are associated with occlusion of an artery or nerve. Furthermore, use of the cannula has been shown to be associated with reduced bruising, ecchymosis, and erythema and to encourage faster recovery. Use of the blunt tip microcannula in the temple to reduce the risk of temporal nerve damage has been suggested. However, this application is not likely to be effective, given the difficulty of inserting a cannula through the temporalis fascia. Cannulas cannot be used for superficial placement and management of fine lines.

Further systematic study is needed to assess the claims of superior safety associated with blunt tip microcannulas. Use of microcannulas at this time may be injector dependent and could vary depending on the anatomic site of treatment. For example, use of microcannulas for injection of the hands has been widely advocated. Although not supported by any evidence available in the published literature, there are anecdotal reports to suggest that HA fillers may be more persistent in low-mobility anatomical sites, such as the temples and tear troughs, relative to more animated sites, such as the nasolabial folds.

The issue of mobility and animation may be relevant to outcomes in the short term. There is nothing in the literature, in the product labeling, or in injector training materials that indicates patients should refrain from facial animation after injection with HA fillers. However, some injectors advocate such activity restrictions for anywhere from an hour up to one day post-injection. Additionally, some injectors advise patients not to sleep with their face pressed to a pillow (opting for a supine position) to further reduce the risk for product migration.

Hyaluronidase is established as the intervention of choice for removal of unwanted deposition of HA and potentially to reduce AEs, such as lumpiness or granuloma formation. There is no standard for use of hyaluronidase (Vitrase, Bausch + Lomb); protocols vary among injectors. Dilution of hyaluronidase in a 1:1 to 1:3 ratio with saline or lidocaine appears to be the norm and is acceptable in the view of this panel. Dilution of hyaluronidase reduces the incidence of erythema and irritation, which is common upon injection of undiluted agent. The advantage of dilution with lidocaine is reduction of injection discomfort. Substantial disintegration of HA is evident within 24 hours with complete dissolution within a week; clinical experience indicates that substantial disintegration may be seen within minutes.

Allergic reactions to hyaluronidase have been reported, although these are predicted to be rare. History of allergic reaction to bee stings may predict sensitivity to hyaluronidase, so questioning patients regarding a history of bee-sting allergy is suggested. Skin testing is not required prior to hyaluronidase injection but may be undertaken.

Enough hyaluronidase should be injected to provide a notable dissipation of product. It should be noted, and patients may be educated about the fact that, degrading injected hyaluronic acid—essentially creating free HA at the injection site—may attract water and produce short-term erythema. Patients should return to the office in a week for follow-up assessment, at which time repeat hyaluronidase injection may be provided, if needed.

Theoretical concerns that injection of hyaluronidase will deplete endogenous HA, causing a severely deflated or atrophied look have not been borne out by clinical experience, and there are no reports of atrophy in the literature. Alternatives to hyaluronidase to address lumps and bumps include massage, needle aspiration, or excision.

**COMBINATION APPROACHES**

There are limited published data from large controlled trials of injectable devices in combination with each other, along with neurotoxins, or in conjunction with energy-based procedures. Several papers describe potential strategies for treatment that have been successfully employed. There are no compelling data that consecutive injection of fillers into the same anatomic area will result in increased incidence of untoward outcomes. In fact, one review suggests that there is little to no risk.

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ANTICIPATED DEVELOPMENTS

Several novel fillers are in development worldwide. In the US, two agents are currently under FDA review. The US Food and Drug Administration General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee voted unanimously in May 2013 to support approval of Juvederm Voluma XC (Allergan). The agent is seeking PMA approval “for cheek augmentation to correct age-related volume deficit in the mid-face,” a novel indication in the realm of facial injectables.

Also under FDA review is Teosyal Redensity (HA, Teoxane), an HA filler available in European markets. In addition to hyaluronic acid, the formulation also contains “Dermo-Reconstructing Complex,” which contains amino acids, antioxidants, minerals, and vitamins that the company describes as intended to support the skin structure and improve radiance.

CONCLUSION

As soft tissue filler injections continue to grow in popularity, continued inquiry into their mechanisms of action, durability, and safety profiles will be essential in allowing clinicians to optimize their use. By examining the wide range of issues related to the use and study of these agents, we have outlined a snapshot of fillers covering the current scientific understanding and practical application. These discussions illustrate the complexity and new potential uses and directions in understanding fillers, particularly HA-based formulations, which have demonstrated significant clinical benefit through reversibility, versatility, and safety. Ongoing and future studies will hopefully yield increasingly nuanced and enhanced understandings of and applications for these unique and powerful agents.

1. Dermatologic fillers are FDA-regulated medical devices requiring PMA approval which:
   a. Is identical to the regulatory approval process for prescription drugs
   b. Typically involves large approval studies with thousands of patients per device
   c. Is the required process of scientific review to ensure the safety and effectiveness of Class III devices
   d. All of the above

2. In addition to wrinkle filling use, recent evidence suggests which useful properties of dermatologic filling agents?
   a. Neocollagenesis activity
   b. Lifting effects
   c. Volumizing effects
   d. All of the above

3. Free HA is:
   a. The white powder form of hyaluronic acid supplied to manufacturers
   b. A clear viscous liquid form of hyaluronic acid dissolved in water
   c. The form of hyaluronic acid following the use of chemical crosslinking
   d. None of the above

4. Which of the two crosslinking chemicals approved for use in the US is used with marketed HA fillers?
   a. 1,4-butanediol diglycidal ether (BDDE)
   b. di-vinyl sulfone (DVS)

5. Which of the following is true regarding the formation of an HA gel?
   a. It results from crosslinking binding HA polymer chains together to produce polymer networks
   b. Increasing degrees of crosslinking decreases the firmness of the HA gel
   c. HA gel may be sieved in order to create molecules of sufficiently small size for injection
   d. A and C

6. Recent research suggests that neocollagenesis properties of HA fillers may lead to:
   a. Increased age-related collagen fragmentation
   b. Enhanced structural support of the dermal extracellular matrix (ECM)
   c. Increased fibroblast shrinkage
   d. Reduced collagen production

7. Evidence suggests that repeat treatments with injectable HAs may lead to longer durations of effect and need for reduced volumes of agent to achieve desired results.
   a. True
   b. False

8. All of the pivotal trials for HA fillers reported some incidence of the superficial bluish discoloration known as the Tyndall effect.
   a. True
   b. False

9. The most commonly reported adverse events relating to HA fillers are:
   a. Granulomatous foreign-body reactions
   b. Persistent nodules
   c. Injection site reactions
   d. The Tyndall effect

CME QUESTIONS

Did the program meet the following educational objectives?

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<th>Objective</th>
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<td>Identify various uses of injectable fillers, their associated treatment regimens, and manage adverse events</td>
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<td>Effectively educate patients about known risks associated with cosmetic therapies</td>
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<td>Utilize cosmetic treatment procedures that result in patient satisfaction, low risk-benefit ratio, and improved quality of life for patient</td>
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