

Pearls on Fillers and Combination Cosmetic Therapy

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Skin aging is a multifactorial process characterized by exogenous and endogenous factors that result in volume loss, rhytide formation, pigmentary alterations, and vascular changes. To achieve more global rejuvenation, a combination of cosmetic therapies can be utilized to target different components of aging skin. This article discusses pearls on using fillers for soft tissue augmentation as well as the benefits of their combined use with botulinum toxin type A (BTX-A) and laser or light therapies as adjunctive cosmetic treatments.

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Skin aging is a complex multifactorial process that is influenced by exogenous and endogenous factors resulting in volume loss, rhytide formation, pigmentary alterations, and vascular changes. A variety of cosmetic modalities can be used to target each of these changes to achieve more comprehensive rejuvenation. Scientific advancements in devices and medical cosmetic therapeutics have allowed noninvasive cosmetic modalities such as dermal fillers, botulinum toxin, and lasers to replace surgical procedures as first-line cosmetic rejuvenation techniques. This article focuses on fillers used in combination with

botulinum toxin type A (BTX-A) and laser or light therapies to achieve optimal rejuvenation.

AGING SKIN

Volume Loss

A major element in the aging face is the loss and redistribution of subcutaneous fat. As we age, gradual volume depletion occurs in the brow areas, temporal fossa, pre-malar and perioral areas, and chin (Figure 1A). The infra-orbital hollow is a groove just beneath the lower eyelid that forms when the suborbicularis oculi fat pad protrudes outward in conjunction with infraorbital dermal atrophy. Beneath the infraorbital hollow is the tear trough deformity. The contours resulting from the tissue protuberance just beneath the infraorbital hollow and tear trough deformity form the so-called double bubble appearance (Figure 1B).

The tear trough, also known as the nasojugal groove, is a natural depression that extends inferolaterally from the medial canthus to approximately the midpupillary line. When the tear trough becomes more prominent and unsightly with age, it is known as a tear trough deformity. The tear trough deformity is not necessarily a consequence of aging, as a mild tear trough deformity also may develop in younger patients. Although it was first described more than half a century ago, there still is no consensus regarding the anatomical cause of the tear

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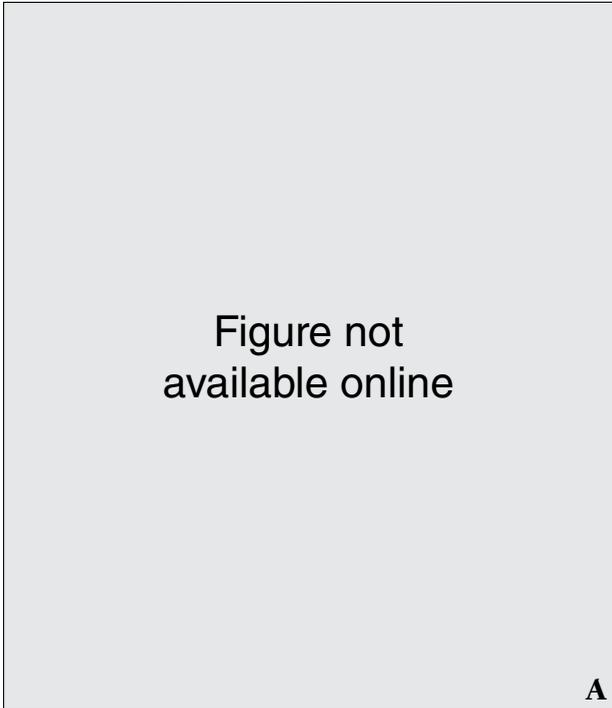


Figure 1. Age-related volume loss in the brow, temporal fossa, pre-malar and perioral areas, and chin (A). The contours of the “double bubble” appearance resulting from tissue protuberance just beneath the infraorbital hollow (top arrow) and tear trough deformity (bottom arrow)(B).

trough deformity among the surgical community.¹ As a result of various and sometimes conflicting anatomical explanations, many surgical procedures have been proposed and performed in attempts to alleviate the deformity, including the release of the orbicularis oculi muscle origin, blepharoplasty, orbital fat excision, transposition of pedicled orbital fat, and midface lifting. Although the cause of the tear trough deformity likely is multifactorial, subcutaneous fat loss has been recognized as the predominant factor.¹⁻³ Other age-related factors that may play a role in accentuating the tear trough deformity include herniation of orbital fat above the deformity; inferior shifting of the structures below the deformity such as the malar fat pad (midface descent); and skin laxity.^{2,3}

Rhytides

Rhytides, both dynamic and static, also contribute to facial aging. With cumulative UV light exposure, the accumulation of abnormal elastic tissue in the dermis reduces the skin's elasticity and impairs retightening, leading to rhytide wrinkle formation. In the early stages of photoaging, rhytides appear only with dynamic facial movement and are imperceptible when the face is at rest. These dynamic rhytides often first appear in the areas of the lateral canthi as crow's-feet, near the oral commissures, parallel to the nasolabial folds, over the zygomatic arch, and over the malar eminences. With more advanced photoaging and repetitive muscle contractions, the rhytides begin to persist even when the face is at rest.

Pigmentary Changes

In addition to rhytide formation, chronic sun exposure also can lead to pigmentary changes in the skin. In general, chronological skin aging is associated with a reduction in melanocyte density.^{4,5} With every decade past 25 to 30 years of age, the number of enzymatically active melanocytes as detected by the dopa reaction decreases by 10% to 20%.⁵ In chronically sun-exposed skin, however, the density of melanocytes actually is increased by approximately 2-fold and the dopa positivity of individual melanocytes also is consistently greater than sun-protected skin.⁴ Furthermore, pigmentation in aging sun-exposed skin is more unevenly distributed than in younger sun-exposed skin.⁶

Vascular Changes

Vascular alterations in the skin occur from UV light exposure, but the changes differ depending on the duration of sun exposure. In chronically sun-exposed skin, vessels become obliterated, particularly in the upper dermis. This reduction of vasculature also is exhibited in aging sun-protected skin.⁷ In contrast, skin that has been

more acutely irradiated by UV light demonstrates vascular hyperpermeability, dermal blood vessel dilation, and angiogenesis.⁷⁻⁹ The resulting enhanced erythema that is clinically apparent in the skin further contributes to the aged appearance of facial skin.

Because of the multifactorial nature of skin aging, non-invasive facial rejuvenation techniques have evolved to accommodate the new paradigm of using combination cosmetic therapies to target the different factors that contribute to aging. These noninvasive cosmetic procedures include a combination of fillers for soft tissue augmentation, botulinum toxin, and various light and laser treatment modalities.

SOFT TISSUE AUGMENTATION

Dermal and subcutaneous fillers effectively treat volume loss and static rhytides that occur with facial aging. Hyaluronic acid (HA) fillers currently are the most widely used fillers in soft tissue augmentation because of their effectiveness, ease of administration, safety profile, and reversibility with hyaluronidase; they also are versatile, as different HA fillers are suitable for correcting fine lines, creases, and scars when injected into the superficial to mid dermis as well as deeper folds when injected into the deep dermis. Hylaform (Hylaform, Hylaform Plus; Genzyme Corporation), Juvéderm (Juvéderm Ultra, Juvéderm Ultra Plus, Juvéderm Ultra XC, Juvéderm Ultra Plus XC; Allergan, Inc), Restylane (Restylane, Restylane-L; Medicis Aesthetics, Inc), Perlane (Perlane, Perlane-L; Medicis Aesthetics, Inc), Prevelle Silk (Mentor Corporation), and Hydrelle (Anika Therapeutics, Inc) injectable gels are indicated for the correction of moderate to severe facial rhytides and folds such as nasolabial folds; Restylane also may be used for lip enhancement. Other fillers currently approved by the US Food and Drug Administration include calcium hydroxylapatite (CaHA) for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and poly-L-lactic acid (PLLA) for correction of shallow to deep nasolabial fold contour deficiencies and other wrinkles, which are both semipermanent fillers, and polymethylmethacrylate for correction of nasolabial folds, which is a permanent filler.

Pearls on Using HA Fillers

When administering any type of filler for soft tissue augmentation, it is critical for the injector to understand the depth within the skin at which a particular product should be injected and be comfortable with the various depths within the dermis and subcutis. When using HA fillers to correct fine lines and rhytides, injections should be made within the superficial to mid dermis. For

deeper rhytides and scars, the injection plane should be at the mid to deep dermis. When correcting deep folds, HA fillers should be injected into the deep dermis to subcutaneous plane.

Many different techniques can be utilized when injecting HA fillers, the most popular being linear threading, serial puncture, fanning, and cross-hatching. These techniques often are implemented in areas such as the nasolabial folds and marionette lines. When using HA fillers, we prefer to use the serial puncture technique with microinjections of filler for nasolabial folds, marionette lines, mental creases, tear trough deformities, and fine lines near the oral commissures or cutaneous lips. This technique provides more precise placement of the product and allows for better control over the amount of filler that is injected into the dermis, while helping to prevent inadvertent overcorrection. Furthermore, the depth of a particular crease or fold may not be uniform along its entire length; thus the amount of filler needed for correction may vary along its length. The serial puncture technique promotes more accurate correction by being able to inject more filler into specific areas with deeper crevasses; it results in a softer appearance that does not look overdone (Figure 2). However, care must be taken when using this technique in patients who are on anticoagulants, as multiple punctures increase the risk for bruising.

The serial puncture technique with microinjections of filler also allows for fuller layering of HA throughout the dermis to correct both deep and superficial folds, giving a better aesthetic result. To correct the deep component of the tear trough deformity, the injection plane should be at the level of the periosteum, given the thinness of the periorbital skin that increases the risk for nodularity and lumpiness if the filler is injected too superficially. Again, we prefer to use the serial puncture technique with microinjections of filler just above the periosteum to add volume, thus minimizing the tear trough deformity. To further correct the more superficial creases of the tear trough deformity, we then dilute the HA filler with lidocaine (with or without epinephrine) in a 1:1 ratio and inject the diluted filler more superficially into the mid to deep dermis to further soften the tear trough deformity. Hyaluronic acid fillers can be diluted either with lidocaine or sterile normal saline, though we prefer lidocaine, as it provides further anesthesia, even when using an HA filler that already contains lidocaine. With the microinjection technique, the injector is able to layer the HA filler at different levels of the mid to deep dermis, thereby producing a more natural filling effect. By administering a diluted HA filler more superficially in the infraorbital area, there is less risk for nodularity, especially when combined with



Figure 2. A patient before (A) and after hyaluronic acid filler injections in the nasolabial folds, oral commissures, marionette lines, mental crease, and lower lip (B).

the microinjection technique that delivers only microaliquots of filler.

To correct fine lines and superficial rhytides, such as those along the upper and lower cutaneous lips, HA fillers should be injected into the superficial to mid dermis. When we are already using an HA filler that is designed to be injected into the mid to deep dermis for rejuvenation of deeper rhytides, we prefer to use the remaining portion of the HA filler for superficial rhytides by diluting it with lidocaine in a 1:1 ratio; the diluted product can then be injected into the superficial to mid dermis using the serial puncture microinjection technique with a low risk for nodularity.

The advent of using fillers for the off-label use of volume replacement rather than just correction of rhytides and folds has become an important element in global facial rejuvenation. This concept also is known as global fillers or liquid face-lift. When working with HA fillers, volume can be achieved by using multiple syringes of HA filler. Taub et al¹⁰ reported a single-center prospective study on the effect of multisyringe HA facial rejuvenation on perceived age. In this small study, 6 to 8 mL of HA filler were injected into the lower two-thirds of the face in 10 women aged 42 to 59 years. Standardized photographs were taken of the participants at baseline and weeks 2 and 4. Three blinded cosmetic dermatologists as well as the participants rated the participants' age in these photographs. There was

an average of 6.1 and 7.3 years of reduction in perceived age at weeks 2 and 4, respectively, among the blinded dermatologists. Similarly, the participants also reported a substantial average reduction in their perceived age of 7.8 and 9 years at weeks 2 and 4, respectively. The authors noted that although CaHA and PLLA fillers last longer than HA fillers and are used more often for full-face volume restoration, both are less versatile than HA fillers. Calcium hydroxylapatite is not recommended for off-label use in the tear trough area or lips but is an excellent filler for volume replacement in other areas. Poly-L-lactic acid also is not recommended for off-label use in the lips and generally requires multiple treatments without immediate results, but PLLA also is considered an excellent choice for severe facial volume depletion. Furthermore, many experienced injectors anecdotally report that smaller amounts of HA fillers are required over time to sustain optimal correction if regular HA filler injection is maintained with smaller volumes.¹⁰

Pearls on Using Non-HA Fillers

Global fillers or liquid face-lifts have emerged as a new precedent for global facial rejuvenation. The use of the semipermanent fillers CaHA and PLLA has been growing in popularity for full-face volume restoration; however, the new paradigm of combination cosmetic therapy

also is emerging with regard to treatment with different filler materials. Layering different fillers can help correct various aspects of facial aging, including volume loss, folds, and rhytides.¹¹ Poly-L-lactic acid is well-known as a volumizer and can be used off-label to treat volume loss in the temples, malar area, and prejowl sulcus.^{11,12} Calcium hydroxylapatite also is often used off-label to restore volume in these areas.^{11,13} The layering of deep tissue HA fillers (eg, Perlane, Restylane) or CaHA for the correction of nasolabial folds, marionette lines, and volume loss in the cheeks, as well as further non-deep tissue HA filler injection for lip augmentation, tear trough deformity, and perioral rhytides (eg, Restylane, Juvéderm), will help achieve more comprehensive facial rejuvenation.¹¹

The aging process also affects the hands. Calcium hydroxylapatite has been increasingly used for the correction of soft tissue loss in aging hands. For injection in the dorsal hands, CaHA can be diluted with lidocaine to create a less viscous material that will produce a softer appearance and allow for easier injection into the appropriate plane.^{14,15} Patients have reported decreased pain associated with the injection when admixed with lidocaine, and there is no evidence that it alters the physical properties of the filler.^{16,17} The amount of lidocaine used for dilution varies among different injectors but may range from 0.5 to 2.0 mL per 1.3-mL syringe of CaHA.^{14,15} The filler can be administered as several boluses in the subdermal plane, while carefully avoiding any vessels, with the skin of the hand pulled up and tented above the injection sites. Following injection, the filler then is massaged and molded to distribute the material evenly throughout the dorsal hand.^{14,18}

COMBINATION THERAPY

HA Fillers With BTX-A

Botulinum toxin is a neurotoxin derived from the *Clostridium botulinum* bacterium. The 7 serotypes of botulinum toxin include types A, B, C (C1, C2), D, E, F, and G.¹⁹ The current US Food and Drug Administration–approved BTX-A products for temporary improvement in the appearance of moderate to severe glabellar lines are onabotulinumtoxinA (Botox Cosmetic, Allergan, Inc), abobotulinumtoxinA (Dysport, Medicis Aesthetics, Inc), and incobotulinumtoxinA (Xeomin, Merz Aesthetics, Inc). Botulinum toxin type A acts as a neuromuscular paralytic agent by cleaving synaptosomal associated with protein of 25 kDa, a protein that mediates fusion of presynaptic vesicles with the plasma membrane of neurons at the neuromuscular junction that allows for the release of acetylcholine.²⁰

The combination of BTX-A and HA fillers is particularly useful in areas where photodamage and repetitive muscular

contractions have resulted in rhytides with both static and dynamic components. Botulinum toxin type A prevents dynamic muscular contractions from further accentuating and worsening static rhytide formation, and the HA filler mends the rhytide or furrow itself. Combination BTX-A and soft tissue augmentation with HA fillers also has been found to act in a synergistic manner, as the adjunctive use of BTX-A in certain facial areas, such as glabellar rhytides, increases the longevity of the filling agent.^{21,22} This combination can be used to treat horizontal forehead lines, crow's-feet, and perioral fine lines.²³

Aging in the infraorbital area can be improved with filler injections to the tear trough deformity, but the addition of BTX-A can further enhance periorbital rejuvenation.^{23,24} Hypertrophy of the pretarsal portion of the orbicularis oculi muscle can result in reduction in the size of the eye opening, further adding to the perception of lower eyelid sagging.²⁴ Botulinum toxin type A in the amount of 1 to 2 U for Botox can be injected 2 to 3 mm below the inferior ciliary margin along the midpupillary line to improve the lower lid contour; however, this procedure should not be performed in patients with lower eyelid laxity, which can be assessed by a snap test, as it may cause further laxity resulting in scleral show.

Combination therapy with BTX-A and HA fillers also can be used for facial recontouring such as brow shaping.²³ A nonsurgical brow-lift may be achieved using BTX-A to block the depressors of the brow, which include the depressor supercillii and orbicularis oculi muscles. An



Figure 3. The combination of botulinum toxin type A and hyaluronic acid filler can be used to achieve a lateral brow-lift. Botulinum toxin type A blocks the orbicularis oculi muscle (indicated by the X), which is a depressor of the lateral brow, and the HA filler is administered 2 weeks later to further enhance the lateral brow-lift (injection sites marked with dots).

HA filler then can be injected in the area of the lateral brow fat pad just below the lateral eyebrow along the superior orbital rim to further enhance the lateral brow-lift and the appearance of brow fullness (Figure 3). Filler injection into this area can be performed either with serial puncture, retrograde injection, or anterograde injection techniques; however, it is critical to stay lateral to the palpable supraorbital notch and not inject into this area where the supraorbital nerve, artery, and vein pass through. When using combination treatment, the filler can be administered 1 to 2 weeks following BTX-A injection so the full effect of the BTX-A can be appreciated before determining how much filler is needed to achieve the desired amount of brow-lift.

In addition to brow shaping, facial recontouring also can be achieved in the zygomatic area using BTX-A in combination with a filler.²³ Young women tend to have a more heart-shaped face; with aging, the zygoma becomes flatter due to a slight loss in facial bone structure, resulting in a less heart-shaped and more aged face. To restore a more youthful appearance, filler can be injected in the region lateral and inferior to the lateral canthus. Adjunctive BTX-A treatment of crow's-feet then can be used to provide additional lift in the upper cheeks to further contour the face.

As combination cosmetic therapy has become a new treatment paradigm, the combination of dermal fillers and BTX-A has grown in popularity for lower face rejuvenation.²⁵⁻²⁷ Traditionally, rejuvenation of the lower face has primarily focused on replacing volume loss in areas such as the nasolabial folds, marionette lines, mental crease, oral commissures, and fine lines of the cutaneous lips; however, similar to the upper face, controlling

excess muscular contraction in the lower face also is cosmetically beneficial to broadly treat the different factors that contribute to the aging face. Botulinum toxin type A can be injected bilaterally into the posterior aspect of the depressor anguli oris muscle just above the mandible to further improve the downturn at the corners of the mouth (Figure 4A), in each side of the mentalis muscle to weaken its contribution to the mental crease (Figure 4B), and in the upper and lower cutaneous lips in the area of the orbicularis oris muscle to improve static rhytides in the upper and lower lips (Figure 4B).^{25,27} The less-experienced injector must be aware that injection of excess BTX-A or injection into inappropriate muscles may result in impaired facial movement.

A study by Custis et al²⁷ examined the effectiveness of a combination of onabotulinumtoxinA and HA filler to treat marionette lines in comparison with HA filler alone. Each of the 22 study participants received combination treatment of the marionette line on 1 side of the face while receiving HA filler with placebo saline on the other side. The authors found that the combination of onabotulinumtoxinA and HA filler resulted in significantly greater aesthetic improvement than the monotherapy-treated side at weeks 2 and 4 upon photographic review with the marionette lines at maximal contraction ($P \leq .05$). Furthermore, the combination therapy side demonstrated a longer duration of 6.5 weeks compared to the monotherapy-treated side with regards to time for return to pretreatment rhytides.²⁷ Similarly, Carruthers et al²⁵ evaluated the effectiveness of treatment with onabotulinumtoxinA and HA filler, either product alone or in combination, for lower facial rejuvenation. The investigators found that the combination



Figure 4. Botulinum toxin type A and hyaluronic acid fillers can be used in combination for lower facial rejuvenation. Botulinum toxin type A injection site (indicated by the X) for the depressor anguli oris muscle, which contributes to the downturn at the corners of the mouth (A). Botulinum toxin type A injection sites (indicated by the X's) for each side of the mentalis muscle of the chin, which contributes to the formation of the mental crease, and the orbicularis oris muscle of the perioral area, which contributes to the perioral static rhytides (B).

therapy achieved superior results according to the cosmetic improvement and global aesthetic improvement scales compared to either modality used alone.²⁵

HA Fillers or BTX-A With Laser or Light Modalities

Laser or light treatments used in combination with dermal fillers and/or BTX-A allows for more global aesthetic improvement in facial aging. Although dermal fillers correct dermal and subcutaneous volume loss and static rhytides of facial aging and BTX-A corrects dynamic rhytides, laser or light therapies help further minimize additional signs of facial aging including fine lines and rhytides, pigmentation, and vascular anomalies seen in chronically sun-damaged skin. The spectrum of current laser or light treatments is vast and includes ablative resurfacing devices (ie, CO₂ laser, erbium:YAG [Er:YAG] laser); nonablative resurfacing devices (ie, 1320-nm Nd:YAG laser); ablative CO₂ and nonablative fractional photothermolysis lasers (ie, 2940-nm Er:YAG laser, 1920-nm and 1550-nm erbium fiber lasers); lasers for pigmentation (ie, Q-switched 532-nm Nd:YAG); lasers for vascular anomalies (ie, pulsed dye laser); and intense pulsed light (IPL), which reduces erythema, telangiectases, and lentigines, and softens facial lines and creases.²⁸

Patients undergoing noninvasive facial rejuvenation often prefer to have multiple cosmetic procedures performed at one time to minimize downtime. However, concerns have been expressed regarding the combination of dermal fillers with laser or light therapies because the heat generated in the dermis could possibly reduce the efficacy or lead to more rapid degradation of dermal fillers.²⁹ Fractional resurfacing lasers, which are becoming increasingly popular, promote neocollagenesis by inflicting dermal wounds, thereby stimulating repair and new collagen production; there is concern that the direct injury inflicted to the dermis also may cause inadvertent damage to the filler material. Many practitioners, therefore, will perform filler injections following laser or light therapy, or wait several days after filler injections to administer laser or light therapy.²⁹

To investigate these concerns, Goldman et al²⁹ conducted a randomized, evaluator-blinded study of 36 patients who were treated with the 1320-nm Nd:YAG or 1450-nm diode lasers, monopolar radiofrequency (RF), or IPL therapy immediately after receiving HA filler injections in the nasolabial folds. In each patient, 1 nasolabial fold and the ipsilateral postauricular area were treated with HA filler injections only, and the contralateral nasolabial fold and postauricular area were treated with HA filler injections immediately followed by the laser, RF, or IPL therapy. The postauricular areas were included as treatment areas because skin biopsies were taken to further evaluate the histologic effects of lasers, RF, and IPL on

the HA gel implants. Although only 8.6% of the biopsy specimens from both the laser/RF/IPL-treated and non-laser/RF/IPL-treated sites contained detectable HA gel implants and thus were considered acceptable for histomorphologic evaluation, no qualitative or quantitative differences in HA gel implants were detectable between the laser-treated and non-laser-treated sites by a blinded, board-certified dermatopathologist. Although these results are from a small sample size, there was no evidence of any disruption or modification of the HA gel implants from combined laser/RF/IPL therapy in the biopsy specimens that were examined. On clinical evaluation, there was no statistically significant difference between laser/RF/IPL-treated and non-laser/RF/IPL-treated sites using the evaluator-assessed wrinkle severity rating scale and the patient self-assessed global aesthetic improvement scale.²⁹

Farkas et al³⁰ examined the effects of common laser and light treatments on HA fillers in a porcine model. In this study, the abdomen of 6 pigs was injected with HA fillers and then subsequently treated with nonablative laser/light or ablative laser devices 2 weeks following filler injection. Histopathologic evaluation of the treated sites demonstrated that implanted HA filler was unaffected by nonablative laser/light therapy and superficial ablative lasers, including 560-nm IPL, the 1064-nm Nd:YAG laser, the 1540-nm nonablative fractional laser, and the CO₂ superficial fractional ablative laser. In contrast, implanted HA filler was demonstrated to be affected by deeper, more aggressive laser treatments, which included the 2940-nm fractional Er:YAG laser and the CO₂ deep fractional ablative laser. The authors concluded that the deep dermal penetration that deeper, more aggressive laser treatments can attain should be taken into consideration before combining them with soft tissue fillers.³⁰

To address the similar concern that adjunctive laser or light therapies possibly affect the efficacy of fillers, Semchyshyn and Kilmer³¹ examined if the use of a nonablative rejuvenation laser, IPL, or RF immediately following BTX-A injections had any effect on the efficacy of BTX-A. The study included 19 participants who received BTX-A injections to either the glabella or crow's-feet area. Half of the BTX-A-treated area was then treated with a nonablative laser, IPL, or RF within 10 minutes of the BTX-A injection. The investigators did not find any decrease in efficacy of the BTX-A in their small study,³¹ but it should be noted that the duration of the BTX-A response needs to be further evaluated.

CONCLUSION

With improved technology and medical care, the population continues to age, thereby increasing the demand for cosmetic therapies for their aging skin. Studies show

that more patients are interested in cosmetic therapies for aging skin. The introduction of innovative noninvasive cosmetic procedures has revolutionized how physicians are able to rejuvenate aging skin. These noninvasive procedures are well-suited for patients young and old who seek less-invasive procedures to achieve rejuvenation.

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