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Global Updates on the Future Directions of Neurotoxins and Fillers

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Summary: Neurotoxins and fillers continue to remain in high demand, comprising a large part of the growing business of cosmetic minimally invasive procedures. Multiple Food and Drug Administration–approved safe yet different products exist within each category, and the role of each product continues to expand. The authors review the literature to provide an overview of the use of neurotoxins and fillers and their future directions. (*Plast Reconstr Surg Glob Open 2016;4:e1177; doi:10.1097/GOX.0000000000001177; Published online 14 December 2016.*)

Cosmetic procedures continue to rise with minimally invasive procedures accounting for the vast majority of the demand. The 2015 American Society of Plastic Surgery plastic surgery report indicates that of the 15.9 million cosmetic procedures, 14.2 million comprised of minimally invasive procedures.[1] Within the cosmetic minimally invasive market, botulinum toxin type A and soft-tissue fillers represent the largest number of procedures. The purpose of this article is to provide an overview of the clinical applications, technical aspects, and future directions of neurotoxins and fillers, endeavoring to provide patients safe and successful outcomes.

NEUROTOXINS

Neurotoxins are products of *Clostridium botulinum* that bind to presynaptic membranes and inhibit acetylcholine release.[2,3] This leads to reversible decrease in muscle contraction. Although various strains of botulinum toxins exist, only 3 types (onbotulinumtoxinA, BoNTA-ONA, or Botox or Botox Cosmetic [Allergan, Inc., Irvine, Calif.]; abobotulinumtoxinA, BoNTA-ABO, or Dysport [Galderma Laboratories, Lausanne, Switzerland]; and incobotulinumtoxinA Xenomin [Merz Pharma, Frankfurt am Main, Germany]) are approved by the U.S. Food and Drug Administration (FDA) for ameliorating the appearance of glabellar wrinkle lines in adults younger than 65 years of age. Botox is also approved for the treatment of crow's feet.

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All 3 neuromodulators should be treated as different products as they differ in the units per vial, composition, and efficacy per unit (Table 1).[4,5] The 3 types are generally constituted in 0.9% sterile, saline (preserved and nonpreserved can be used) with the reconstituted product safely stored for 1 week. The patient's presentation and treatment areas influence the amount of the product injected. Please refer to the proper FDA labeling for details of specific use. Admittedly, all have been shown to be safe and effective for at least 3 to 4 months post treatment.

These products are often employed in off-label format to treat areas outside of the glabella including the upper face, midface, and lower face (Tables 2–5).[5–7] The effects of the neurotoxins last for approximately 3 to 4 months. Adverse complications can arise often because of improper techniques and lack of facial anatomy, leading to pain, inflammation, ecchymosis, erythema, and local weakness.

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Table 1. Comparisons of Various Botulinum Toxin Formulations

Brand Name (Nonproprietary Name)	FDA-approved Indications	Duration of Effect (mo)	Onset of Action (d)	% NAP to Total Protein Content	Dose Equivalent Units	Pain
Type A						
Botox (onabotulinumtoxinA)	Cervical dystonia Strabismus and blepharospasm Rhytides: glabellar lines and crow's feet Severe primary axillary hyperhidrosis Upper limb spasticity Chronic migraines Neurogenic bladder	3–6	3–5	85	1	+
Xeomin (incobotulinumtoxinA)	Cervical dystonia Blepharospasm refractory to Botox Rhytides: glabellar lines	3–6	2–4	0	1	+
Dysport (abobotulinumtoxinA)	Cervical dystonia Rhytides: glabellar lines	3–6	3–5	25	2–3	+
Meditoxin/neuronox/Siax/ Cunox/Botulift	Not approved by FDA (Korea)	*	*	†	1	†
Prosigne	Not approved by FDA (China)	*	*	†	1.5	†
Type B						
Myobloc (rimabotulinumtoxinB)	Cervical dystonia	2–3	1–4	55	30–50	++

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†Limited data available.

NAP, nontoxic accessory proteins.

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Table 2. Consensus Recommendations and Expert Panel Opinion Regarding Combination Treatment of the Upper Face

	Frequency of Treatment with the Same vs Sequential Sessions			
	Same (%)	Sequential (%)	Typical Total Dose of OnabotulinumtoxinA (U)	Preferred Filler
Glabellar rhytides	44	56	12–40 Doses as low as 8 U may be appropriate for some patients	Superficial Vycross or Hylacross Dilution–reconstitution of Hylacross preferred by some panelists
Forehead	45	55	8–25	Rhytides: superficial Vycross or Hylacross Dilution-reconstitution of Hylacross preferred by some panelists Contouring: midlevel or diluted deep volumizer Vycross
Lateral periocular	38	62	6–15 per side	Superficial Vycross

Botulinum toxin dosage recommendations may be extrapolated with care and appropriate dosages to other toxin formulations. The paradigm of layered hyaluronic acid filler implantation is illustrated by representative product selections for deep volumizer, midlevel, and superficial Vycross (Voluma, Volift, and Volbella) and for Hylacross (Juvéderm Ultra). Selections may be extrapolated as appropriate to other hyaluronic acid filler families.

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Table 3. Consensus Recommendations and Expert Panel Opinion Regarding Combination Treatment of the Middle Face

	Same vs Sequential Sessions			
	Same (%)	Sequential (%)	Typical Total Dose of OnabotulinumoxinA (U)	Preferred Filler
Lower eyelid	51	49	0.5–2 per side (infraorbital rhytides)	Supraperiosteal and subcutaneous contouring, eg, nasojugal fold: superficial Vycross
Nose	52	48	1–4 (nasal flare) 2–6 (tip elevation) 4–8 (oblique lines). Doses as high as 10 U may be appropriate for some patients	Deep volumizer or midlevel Vycross
Cheek	61	39	1–6 (intracutaneous, with caution)	Deep volumizer Vycross

Botulinum toxin dosage recommendations may be extrapolated with care and appropriate dosages to other toxin formulations. The paradigm of layered hyaluronic acid filler implantation is illustrated by representative product selections for deep volumizer, midlevel, and superficial Vycross and for Hylacross. Selections may be extrapolated as appropriate to other hyaluronic acid filler families.

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Table 4. Consensus Recommendations and Expert Panel Opinion Regarding Combination Treatment of the Lower Face

	Same vs Sequential Sessions		Typical Total Dose of OnabotulinumtoxinA (U)	Preferred Filler
	Same (%)	Sequential (%)		
Masseter	22	78	15–40	Deep volumizer or midlevel Vycross
Lips/perioral	54	46	1–5	Perioral rhytides: superficial Vycross or Hylacross Dilution-reconstitution of Hylacross preferred by some panelists Lips: submucosal implantation of superficial Vycross or Hylacross
Oral commissure/ marionette lines	68	32	2–4 per side (DAO) Some panelists limit dose to 2 U per side	Deep volumizer Vycross
Jawline and neck	53	47	6–12 per band (platysma) Maximum dose 60 U	Deep volumizer Vycross

Botulinum toxin dosage recommendations may be extrapolated with care and appropriate dosages to other toxin formulations. The paradigm of layered hyaluronic acid filler implantation is illustrated by representative product selections for deep volumizer, midlevel, and superficial Vycross and for Hylacross. Selections may be extrapolated as appropriate to other hyaluronic acid filler families.
DAO, depressor anguli oris.
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Table 5. Hyaluronic Acid Fillers

	Density	Injection Level	Anticipated Duration	FDA-approved Use	Target Areas
Belotero Balance	Moderate	Superficial dermis	6 mo	Smooth wrinkles, NLF*	NLFs, perioral rhytids
Hydrelle (Elevess)	High	Mid to deep dermis	Up to 12 mo	Moderate to severe facial wrinkles	NLFs, lip augmentation
Juvederm Ultra	Moderate	Mid to deep dermis	Up to 12 mo	Moderate to severe wrinkles	Temporal hollowing, NLF
Juvederm Voluma	High	Deep dermis to supraperiosteal	Up to 24 mo	Cheek augmentation	Cheek augmentation
Perlane	High	Deep dermis to superficial subcutis	6 mo	Moderate to severe wrinkles	Temporal hollowing, NLF
Prevelle Silk	Low	Superficial dermis	3–4 mo	Lip augmentation, perioral rhytids	Lip volumization, perioral rhytids
Restylane	Moderate	Dermal–epidermal junction	6 mo	Moderate to severe facial wrinkles	Perioral rhytids, NLF, temporal hollowing
Restylane Silk	Low	Superficial dermis	6 mo	Lip augmentation, perioral rhytids	Lip volumization, perioral rhytids

*NLF, nasolabial folds.
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Technical Pearls[3,5,7,8]

- Avoid injecting into the lower aspect of the midbrow to prevent diffusion into the levator muscle causing eyelid ptosis.
- Lateral corrugators must be injected 1 to 2 cm above the orbital rim to avoid the Mephistos sign (quizzical look).
- Crow's feet must be injected superficially (subdermal), 1 cm lateral to the orbital rim, and above the zygoma to avoid diplopia, ectropion, and ecchymosis.
- The perioral region must be injected in small volumes to avoid oral incompetence and speech pathology. This must be done with a profound understanding of the perioral anatomy including the depressor anguli oris.
- Platysma bands should be in small amounts and superficially into the specific platysmal bands only (no more than 100 U Botox in 1 setting) to avoid dysphagia.

Future Directions

In 2000, the first open-label, noncontrolled trial demonstrated BoNTA-ONA as a safe and efficacious modality for acute and prophylactic treatment of migraine headaches. Since then, numerous studies have highlighted the benefit of BoNTA-ONA in addressing chronic migraines.[9–12] The *International Headache Classification* 3rd Edition (Beta Version) defines chronic migraine as a headache occurring on at least 15 days per month for more than 3 months, with features of migraine headache on at least 8 days a month.[13] BoNTA-ONA has also been used in headaches associated with cervical dystonia and tension type and with whiplash, but its role is not as well defined as in chronic migraines.

Furthermore, the use of Microbotox, a technique that involves tiny blebs of Microbotox, refers to the use of a neuromodulator at 0.8- to 1.0-cm intervals into the skin or just below that into the superficial fibers of the facial muscles.[14,15] The purpose is to weaken the superficial muscles, leaving the underlying deeper facial muscles alone. It has been found that this can smoothen and tighten the skin. The technique has been utilized successfully in the upper face and midface[16] and recently in lower face and neck.[14] It also provides the ability to control sweat and sebaceous glands, providing a smoother skin.[5,17] Studies have confirmed Botox as modality to treat palmar hyperhidrosis.

Neurotoxins are being developed including a topical form with clinical trials underway that may obviate the need for injections in specific areas and potentially reduce pain from shots. These products are being trialed for lateral crow's feet, glabellar lines, and hyperhidrosis. Currently, Revance (Newark, Calif.) is conducting clinical trials with its products, RT001 and RT002 (topical BoNTA-ONA), to be used for crow's feet and axillary hyperhidrosis and glabellar lines and cervical dystonia, respectively. Although 1 study does demonstrate favorable treatment of crow's feet using RT001, further scientific data are needed to determine its efficacy in other areas.[18] Other type A products including the Korean versions (Meditoxin/Siax/Neuronox) and Prosigne (Lanzhou Institute of Biological Products, Lanzhou, People's Republic of China) are currently not approved by the FDA but may be in the future pending future trials.[5]

FILLERS

Although various dermal fillers exist, the focus of this article is on the following: hyaluronic acid (HA) products, calcium hydroxyapatite, poly-L-lactic acid, and polymethylmetacrylate.[19] The rise in filler use may be attributable to the paradigm shift from a 2-dimensional view to a 3-dimensional perception of the face, with aging impacted tremendously in the medial aspect by volume loss.[6,20,21] In fact, many cosmetic medicine practitioners are adhering to the mantra of lift laterally and fill medially, acknowledging the profound rejuvenation effect that occurs when placing volume in areas such as the tear trough, malar projection, nasolabial fold, and lips. The powerful combination of neuromodulator and filler therapy can treat hyperdynamic muscle changes and volume loss, restoring facial harmony in the early signing of facial aging.

Currently, there is an evolving family of FDA-approved HA products such as Restylane and Restylane Lyft (Galderma Laboratories, Fort Worth, Tex.), Belotero (Merz Aesthetics, Greensboro, N.C.); and Juvederm Ultra, Juvederm Voluma and Vobella (Allergan, Irvine, Calif.). HA products arise from a naturally occurring polysaccharide found in the skin, cartilage, and connective tissues in mammalian species. This makes it a nonimmunogenic product ideal for use in humans. The products differ on particle size, viscosity, and degree of cross-linking that govern its biological properties and clinical use.

Poly-L-lactic acid (Sculptra; Sanofi-Aventis, Bridgewater, N.J.) gained popularity when approved by the FDA in HIV-positive patients with lipoatrophy of the face. Since then, the product consisting of poly-L-lactic acid microsphere in a powdered form has been used in immune competent patients for soft-tissue augmentation. It creates a foreign body reaction that stimulates fibroblast and type I collagen growth. Patients should be informed that final results often take multiple sessions and can take several months; however, the result may last over a year.

Calcium hydroxyapatite (Radiesse; Merz Aesthetis, Inc., San Mateo, Calif.) works by developing a scaffold for collagen ingrowth. The calcium hydroxyapatite spheres are in an aqueous gel medium that dissolves over several weeks. The nonimmunogenic product stimulates collagen production, enabling volume expansion. These results also may last longer than 1 year.

Polymethylmetacrylate (Artefill; Suneva Medical, San Diego, Calif.) differs in that it is a permanent filler and can have immunogenic issues. The product consists of polymethylmetacrylate particles suspended in a matrix of lidocaine and bovine collagen. Although the collagen gel gives patient the initial volume, as it is resorbed, the polymethylmetacrylate leads to an encapsulation of tissue that is permanent, making changes irreversible. The bovine collagen necessitates a skin test 1 month before its use to determine if allergic symptoms will develop.

These properties determine how much and where in the face these fillers are employed. Various techniques exist in how to inject them including serial puncture, threading, fanning, and cross-hatching.[22] The type of product impacts how it is injected, where it is injected, and what quantity is injected (Table 5).[20] For example, high-viscous and densely cross-linked substances such as Juvederm Voluma and Restylane Lyft are used for malar augmentation, whereas less viscous and lower cross-linked substances such as Belatero, Restylane Silk, and Vobella when injected in a smooth manner can be used for fine lines, wrinkles, and lip augmentation (Tables 2–5).[6]

Technical Pearls[6,20,23]

- Profound understanding of the facial anatomy as it relates to the vasculature is paramount in delivering fillers safely to avoid catastrophic insults, such as blindness and nasal tip necrosis.
- Specific training is essential for each filler and for each area especially for around the nose, lips, and periorbital areas to prevent significant adverse reactions and vascular consequences.
- Fillers can be used conservatively, advising patients that touch-ups will be necessary to avoid overfilling areas.
- Recognize vascular compromise signs such as blanching and abort procedure; be familiar with application of nitropaste and injection of hyaluronidase.

Future Directions

The use of safe and more versatile FDA-approved fillers for restoring volume outside the face as well as for roles outside of volume expansion continues to expand. Recent articles have demonstrated its utility in hand rejuvenation when injected using the appropriate technique.[24,25] Its role in acne continues to be under investigation with further studies necessary.[26] Others have reported its role in chin implants as fillers can soften the transition from the skin to the implant with its volume effect. It can also provide volume to areas for the ear lobule, addressing sagging effects.

Manufactures continue to develop fillers to utilize in various areas by altering their biological composition. As the search for a product that is nonimmunogenic, biodegradable, reversible, and long-lasting, the creation of new fillers and their uses continue to evolve.

CONCLUSIONS

Neurotoxins and fillers remain the highest demanded comestic minimally invasive procedures. Their combined use provides an injector powerful ways to reverse the stigmata of aging, particularly facial hyperdynamic musculature and volume loss. The role they play in other areas outside of the face and treatment of other disorders continues to evolve with further scientific studies need to validate claims. This article endeavors to provide a reference of the use of neurmodulators and fillers, technical maneuvers to mitigate complications, and future directions.

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