HOW TO CHOOSE A FILLER OR NEUROMODULATOR TO TREAT YOUR PATIENTS’ AESTHETIC CONCERNS
Disclosures

Consultant
MERZ PHARMACEUTICAL, US
SUNEVA PHARMACEUTICAL
PROLENIUM US

Previously employed as Medical Science Liaison (MSL) for BioForm/Merz, Galderma, and Suneva (2007 – 2018)
Gerrie Obi, MSN, APRN, AGPCNP-BC, CPSN

Gerrie Obi has over three decades of plastic and aesthetic experience working both in private practice alongside her husband John Obi, MD (ASPS board-certified Plastic & Reconstructive Surgeon) and in the aesthetic pharmaceutical and medical device industry.

She earned a master’s degree in nursing with a specialty in adult and geriatric primary care. Gerrie is a Master level injector and has held positions in several of the major aesthetic corporations serving as an educator and physician liaison providing clinical guidance and working with industry thought leaders, supporting evidence-based research, and commercial launch for various products.

Gerrie is also an international trainer; she trains the trainers as well as other Master injectors, both nationally and internationally. She has trained thousands of aesthetic providers globally over the past decades, as well as provided innovative aesthetic care in Northeast Florida area for countless clients since 1983.

Currently serving as ISPAN Director for Industry Relations and previously served on the ISPAN Scientific Sessions Planning Committee.
Botulinum Neurotoxins (BoNTs)
Botulinum Neurotoxins (BoNTs)

- Eight (8) known serotypes: A- H
- Serotype A is the most potent and only type FDA approved for cosmetic use

3 Types FDA approved
- OnabotulinumtoxinA  Botox
- AbobotulinumtoxinA  Dysport
- IncobotulinumtoxinA  Xeomin

In the future…
Revance Therapeutics
- DaxibotulinumtoxinA = Injectable (topical ?)
Allergan  Acquisitions
- NivobotulinumtoxinA = Medytox (liquid), Korea
- BoNT/E = Bonti, Newport Beach, CA (rapid onset of action within 24 hours and a 2 to 4-week duration of effect)
Botulinum Neurotoxins (BoNTs)

FDA Approved Doses

**OnaBotox:** 20U glabella, 12U at each lateral canthus (crow’s feet), onset in 1-2 days, 3 month duration. Comes in 50U & 100U vials

**AboDysport:** %oU glabella, onset 1-2 days, up tp 4 months duration, 300 U vials

**IncoXeomin:** 20U glabella, onset within 7 days, 3 month duration, 50U & 100U vials
Botulinum Neurotoxins (BoNTs)

- Molecular weight of the BoNT-A varies between 300 and 900 kDa.
- INCO 150 kDa neurotoxin and does not include complexing proteins
-ONA is composed of a 900 kDa complex
- After dilution and reconstitution of the product, all FDA approved neurotoxins rapidly dissociate from the complexing proteins
- Molecular weight (protein complex size) does not influence the biological activity and pharmacological properties of BoNT
- Complexing proteins do not contribute toward diffusion properties, seem not to contribute to the therapeutic effect, and are not required for the stabilization of the neurotoxin in the pharmaceutical formulation
Botulinum Neurotoxins (BoNTs)

Black Box Warning

• 2009 FDA mandate warning (Types A&B) potential spread effect

• Most commonly occurred in children with cerebral palsy treated with high-dose BoNT

• No significant systemic effects have been reported with cosmetic use in recommended areas
Botulinum Neurotoxins (BoNTs)

**Mechanism of Action**
(MOA)

- Inhibits the release of acetylcholine at the neuromuscular junction by binding to the receptor site of a motor nerve terminal in the striated muscles fibers and blocking the muscular transmission.

- Localized muscle activity due to chemo denervation of the muscle. The muscle and the nerve cannot communicate temporarily.

- Results are product in dose dependent.
Botulinum Neurotoxins (BoNTs)

ONA/Botox

- Vacuum dried powder neurotoxin complex, human albumin, and sodium chloride
- PI: reconstitution with preservative free 0.9% saline, 2.5 mL per 100 and new vial. Avoid agitation, use within 24 hours and store at 36 to 46°F and before and after reconstitution. **Do not freeze!**
Botulinum Neurotoxins (BoNTs)

**ABO/Dysport**

300u freeze dried neurotoxin with human albumin, lactose and trace amounts of cow’s milk.  
*DO NOT give if has true milk allergy* – not allergic if just has lactose intolerance

PI: reconstitute with preservative free 0.9% saline. Add 2.5mL or 1.5 mL per 300 U vial, avoid agitation, should be used within 4 hours of reconstitution.
Botulinum Neurotoxins (BoNTs)

INCO/XEOMIN

• 50U to 100U vial talk soon, human albumin and sucrose. Clean toxin with no accessory proteins

• PI: reconstitute with appropriate amount of preservative 0.9% saline, avoid agitation (vial should be gently swirled and turned upside down to mix ALL powder particles). Should be used within 24 hours of reconstitution. Store at room temperature prior to reconstitution and at 36 to 48°F after reconstitution.
Botulinum Neurotoxins (BoNTs)

Consensus Guidelines

- Less painful = use preserved saline
- Duration and results are dose related
- Mild agitation of vial is ok
- BoNT can be stored up to 6 weeks refrigerated and still have efficacy
Botulinum Neurotoxins (BoNTs)

- All wrinkling is perpendicular to the muscle; the ying and yang of the muscles
- Stronger muscle and deeper rhytids = increased dosing
- Note asymmetries *prior to treating* patient
Botulinum Neurotoxins (BoNTs)

**Mechanism of Action**

- Botulinum Toxin Type A blocks transmission of acetylcholine (ACh) from neuron to muscle

- Inhibits muscle contraction and causes muscle paresis (weakness) or paralysis

- Botulinum Toxin Type A only affects "cholinergic neurons" (neurons which use acetylcholine as a neurotransmitter)
Botulinum Neurotoxins (BoNTs)

MICROBOTOX

- 20 units in 1 mL of solution (equivalent to reconstituting a bottle of Botox with 5.0 mL saline and then directly drawing out 1 mL)

- More convenient to use Botox from a bottle of 100 units that has been reconstituted with 2.5 mL of saline (standard dilution). In patients with thin necks, a dilution of 20 units per mL solution is sufficient.

- In patients with visibly thicker skin a concentration of 28 units per mL solution may deliver better results

DERMAL FILLERS
Dermal Fillers

United States Food and Drug Administration (US FDA) *dermal fillers* (a.k.a. injectable implants or soft tissue fillers) are considered *medical device implants* for use in helping to create a smoother and/or fuller appearance in the face, including nasolabial folds, cheeks and lips and for increasing the volume of the back of the hand.

- **Classification**
  - **Duration**
    - short-term
    - long-lasting
    - permanent

- **Physical characteristics (absorbable & non-absorbable)**
  - nonparticulate: hyaluronic acid
  - Particulate: calcium hydroxylapatite (CAHA), ploy-lactic acid (PLLA), & polymethylmethacrolate (PMMA)
TEMPORARY DERMAL FILLERS

Hyaluronic Acid

• A type of sugar (polysaccharide) present in body tissues
  • skin
  • cartilage

• Able to combine with water and swell when in gel form, causing a smoothing/filling effect

• Sources of hyaluronic acid used in dermal fillers
  • bacteria
  • rooster combs (avian)

• Chemically modified (crosslinked) to make it last longer in the body
  • effects of this material last approximately 6 – 12 months
How to differentiate each HA filler

In order to create a HA filler with unique properties and characteristics, specific variables can be modified

• Total HA concentration
• Soluble HA added or not crosslinked (lubricant)
• Average molecular weight (MW) of HA (length of strands)
• Degree of cross-linking or cross-linker used
• Varying particle size
• Gel / Fluid HA ratio
• ‘Intrinsic’ viscosity is essentially a measure of a polymer’s molecular weight

• Longer HA chains have higher molecular weight and require less cross-linker (BDDE)

• Shorter HA chains have lower molecular weight and require more BDDE to achieve effective links

• In essence, more BDDE makes the HA chains thicker and less like native HA and is less biocompatible within the body increasing the likelihood of adverse reactions and macrophage activation
  • HMW-HA has shown the ability to attenuate the inflammatory response
  • LMW-HA and MMW-HA have shown increased expression of macrophage inflammatory proteins and monocyte chemotactic proteins

• More BDDE makes the HA chains less able to absorb or uptake water after implantation (hydrophilic)
Molecular Weight (MW)

- Determined by length of HA strands (# of repeating disaccharide units linked together)

- Weight of the strands of HA (kiloDaltons, kDa)

- Only measured for soluble HA

  → The longer the HA strand, the higher the molecular weight

Amount of cross-linking depends on many factors

(ie: manufacturing processes)
## Comparison of US FDA HA Fillers

<table>
<thead>
<tr>
<th>Company</th>
<th>HA content (mg/mL)</th>
<th>% Soluble HA</th>
<th>% HA &lt;250 kDa</th>
<th>% HA &gt;250 kDa</th>
<th>Cross-linker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belotero</td>
<td>Merz</td>
<td>22.5</td>
<td>58.8</td>
<td>26.8</td>
<td>73.2</td>
</tr>
<tr>
<td>Restylane</td>
<td>Galderma</td>
<td>20</td>
<td>25.9</td>
<td>65.4</td>
<td>36.4</td>
</tr>
<tr>
<td>Restylane Defyne</td>
<td>Galderma</td>
<td>20</td>
<td>34.5</td>
<td>67.7</td>
<td>32.3</td>
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<tr>
<td>Juevderm Ultra</td>
<td>Allergan</td>
<td>24</td>
<td>36.0</td>
<td>58.3</td>
<td>41.7</td>
</tr>
<tr>
<td>Juevderm Ultra Plus</td>
<td>Allergan</td>
<td>24</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Versa</td>
<td>Prollenium</td>
<td>25</td>
<td></td>
<td></td>
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</tbody>
</table>
Rheology of HA

TEXTURE: $G'$ & $G''$

- Elastic Gel
  - Jello-Like
  - Stores Mechanical Energy like a Spring

- Viscous Liquid
  - Honey-Like
  - Dissipates Mechanical Energy by Friction

- Visco-Elastic Mixture
  - Hybrid Mechanical Properties
The measure of elasticity is called the storage modulus or $G'$

Generally, for many materials, the higher the deformation rate the more solid-like the material (Jello-like) and the higher the value of $G'$.

Higher cross-linking generally leads to higher $G'$, but this also leads to gels which absorb less or no fluid on implantation.
G’ Elastic Modulus

- Revanesse® Versa™: 130
- Restylane®: 650
- Juvederm® Ultra Plus: 100
- Juvederm® Ultra: 160

Elastic Gel Jello-Like (elastic)
VISCOSITY

• Cross-linking will increase the viscosity, but not necessarily the extrusion force

• At higher levels, an increase in cross-linking can lead to lower viscosity

• With an increase in cross-linking, there are less potential HA interactions with other HA strands, thereby decreasing the extrusion force

• Persistence of cross-linked HA fillers in the skin is proportional to both concentration and elasticity (stiffness) of the gel
Cross-link density: number of cross-links per available site for cross-linking on a strand of HA

**Low cross-link density**

- Lower gel stiffness
- Increased gel stiffness

**High cross-link density**

- Decreased space between cross-linker
PERCENTAGE CROSS-LINKING

<table>
<thead>
<tr>
<th>Product</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revanesse® Versa™</td>
<td>7%</td>
</tr>
<tr>
<td>Restylane®</td>
<td>1.20%</td>
</tr>
<tr>
<td>Juvederm® Ultra Plus</td>
<td>11%</td>
</tr>
<tr>
<td>Juvederm® Ultra</td>
<td>9%</td>
</tr>
</tbody>
</table>
G” Viscous Modulus

Viscous Liquid Honey-Like (flow)

- **Revanesse® Versa™**: 32
- **Restylane®**: 106
- **Juvederm® Ultra Plus**: 38
- **Juvederm® Ultra**: 35
EXTRUSION FORCE

- Revanesse® Versa™: 3
- Restylane®: 1
- Juvederm® Ultra Plus: 5.1
- Juvéderm® Ultra: 2.7
DEGRADATION TEST

Hyaluronidase Enzyme Solution

Mix

Rheometry

G' vs Time
Normalized Degradation Profiles of Dermal Fillers

- Versa
- Juvederm Ultra +
- Restylane
The aspect ratio measures how spherical a particle is. To be a perfect sphere, the length and width of the particle should match. Following this method, the aspect ratio of a perfect sphere is 1.0. The batch of Revanesse® VersaTM tested for this study was composed of over 68% perfectly spherical particles.
Juvéderm® Ultra Plus is a registered trademark of Allergan. Revanesse® Versa™ is a registered trademark of Prolleum Medical Technologies Inc. Restylane® is a registered trademark of Galderma Laboratories, L.P.
GEL SWELLING

- HA is hydrophilic and absorbs water post injection, which causes the gel filler to swell.
- Depends on water content (equilibrium) before injection. Fully-hydrated HA gel (“at equilibrium”): fully saturated with water.
- Under-hydrated HA fillers: can still uptake more water, will swell after injection.
Prolleumium Gel Dialysis

• All HAs have the ability to bind to water, and the more cross-linked the product is, the less “room” there is for water as the sites are bonded to BDDE.

• VERSA does not “swell” is because the pH and osmolality of the gel are balanced to that of the body.

• Dialysis is performed on Prolleumium gels for 7 days after manufacturing for two reasons:
  • 1. to wash off any excess BDDE or unwanted chemicals/toxins.
  • 2. The gel is allowed to sit in "body conditions" for 7 days.

• This process allows the Prolleumium gels to bond to water during dialysis as they would in tissue before being packaged rendering the finished product to be "primed" for integrating into the body, and is less likely to take on any additional water, preventing over correction.
Where are most HA fillers injected?

“Dermal” Fillers?

- Historically designated for injection into the dermis by FDA
- The dermis varies widely in thickness by area (1-4 mm)
- It is nearly impossible to determine the depth of injection:
  - Due to thickness of needles
  - Angle of needle placement
- Many HCPs believe they inject HA fillers intradermally, but most are probably depositing in the subcutaneous space.
PARTICULATE FILLERS

Calcium Hydroxylapatite (CAHA) Radiesse™

- FDA approval for wrinkle filling in the face or volume loss in hands
- Particles are suspended in a gel-like solution (carboxymethylcellulose) and injected into the wrinkle in the face or under the skin in the dorsom of the hand.
- The effects of this material last approximately 18 months. While in the body, calcium hydroxylapatite will be visible in x-rays and may obscure underlying features.
PARTICULATE FILLERS

- Poly-L-lactic acid (PLLA)
  PLLA is a biodegradable biocompatible man-made polymer. This material has wide uses in absorbable stitches and bone screws.

- PLLA is a long-lasting filler material that is given in a series of injections over a period of several months. The effects of PLLA generally become increasingly apparent over time (over a period of several weeks) and its effects may last up to 2 years.

sculptra®
poly-L-lactic acid
NON-ABSORBABLE FILLERS

Polymethylmethacrylate microspheres (PMMA microspheres)
• Non-biodegradable, biocompatible, man-made polymer.
• Used in other medical devices (bone cement and intraocular lenses)
• PMMA is tiny, round, smooth particles that are not absorbed by the body.
• When used as a soft tissue filler, PMMA beads are suspended in a gel-like solution that contains cow (bovine) collagen and injected into the face.
PLATELET RICH PLASMA (PRP)
PLATELET RICH FIBRIN (PRF)
Platelet Rich Plasma or PRP

- Refers to platelets in plasma, the platelet concentration in plasma is generally considered to be twice the normal concentration in whole blood.
PRP/PRFM

- When PRP is injected into the dermis, it turns to PRFM when exposed to collagen in the skin.
- Processed PRFM = 10% calcium chloride or calcium gluconate + / 90% PRP.
- PRP = liquid injectable (diffuse area).
- PRFM = gel injectable (used in smaller area to avoid diffusion).
PRP/PRFM

- Subtle fill with qualitative improvement of skin tone and texture
- “brightens” the infraorbital region
- Downtime is about 48 hours of puffiness. The procedure takes only 20 minutes
- Autologous filler, appealing to many patients because it as natural
PRP/PRFM

SELPHYL®

Provides:
• Moderate volume
• Improved blood supply
• Collagen stimulation

Results:
• Improves skin texture and color
• There are no residual effects, and the material is undetectable
COMMERCIALY AVAILABLE PRP SYSTEMS

JP200
GLO PRP
Magellan Autologous Platelet Separator System
KYOCERA Medical PRP Kit
SELPHYL
XCell
MyCells

• Large differences both between and within the studied PRP separation systems were found for all the growth factors.

• Preparation protocols and prices varied widely between systems.
Platelet Rich Fibrin or PRF

- PRP with the addition of a precise amount of calcium chloride or calcium gluconate, which initiates the conversion of fibrinogen to fibrin, as part of the clotting cascade
  - The fibrin matrix serves as a three dimensional scaffold to maintain the platelets at the site of injection
  - The scaffold also serves to protect the platelets so their release of growth factors can be sustained over a longer period of time

When injecting PRF use same precautions as when using other soft tissue filler.
Almost everyone can benefit from PRP/PRF, but not everyone will benefit the same way.

- Patients of all ages are good candidates, including younger patients in their 30s and early 40s.

- For those who start rejuvenation treatment before lines become deeply etched and the skin too lax, PRP/PRFM is an ideal preventative and corrective injectable treatment.

- If folds develop due to volume loss, then a filler mixed with PRP/PRFM will provide immediate results.
A burst of growth factors from SELPHYL® stimulates the creation of new tissue, especially collagen, elastin, and blood vessels, like those found in younger, resilient skin.
MIXING PRP/PRFM WITH DERMAL FILLERS

• Mixing PRP/PRF into a soft tissue filler allows the injector to specifically tailor the filler to meet the treatment needs

• PRP in liquid form will lower the HA concentration and make the filler more viscous and less cohesive.

• PRP/PRF stimulates neocollagenesis and when mixed with fillers the patient will receive instant volumization AND will have dermal rejuvenation that will develop over the next couple of months

• PRP/PRF has antimicrobial characteristics and could lessen the possibility of post injection infections
Mixing PRP/PRF + Fillers + BoNT and injecting into the superficial dermis will enhance the texture and pigmentation of the skin decreasing rhytids, uneven skin texture, and hyperpigmentation concerns.

Delivery Methods:
• Microneedling
• Aqua Gold
  • Micro channel and deliver treatments directly to the skin.
  • Structural integrity of the microneedle from surgical grade stainless steel
  • Pure gold has high biocompatibility with human skin, preventing irritation and allergic responses after use. Impurities and other metals may result in unnecessary irritation.
The Aging Face

- Brow ptosis
- Skin laxity with hooding upper lid
- Bagging of the lower lid
- Perioral rhytids (wrinkles)
- Marionette lines
- Jowls
- Forehead rhytids (wrinkles)
- Glabellar frown
- Tear trough deformity
- Elongation and flattening of upper lip; thinning of vermillion
- Chin ptosis
- Platysma bands
Thank you!
Oudelaar BW¹, Peerbooms JC², Huis In 't Veld R¹, Vochteloo AJH¹.