Since onabotulinumtoxinA for nonsurgical aesthetic enhancement of glabellar lines was initially reported, the popularity of botulinum neurotoxin (BoNT) products among both clinicians and consumers has rapidly grown, and we have seen several additional BoNT formulations enter the market. As the demand for minimally invasive cosmetic procedures continues to increase, we will see the introduction of additional formulations of BoNT products as well as new delivery devices and administration techniques. In this article, we provide a brief update on current and upcoming BoNT products and also review the literature on novel administration methods based on recently published studies.

(eg, cervical dystonia, strabismus, blepharospasm, headache, urinary incontinence) in the United States: abobotulinumtoxinA, incobotulinumtoxinA, onabotulinumtoxinA, and rimabotulinumtoxinB. The FDA-approved dermatologic indications (eg, moderate to severe glabellar or canthal lines, severe axillary hyperhidrosis) for these products are provided in the Table. On a global scale, there are several other commonly utilized formulations of BoNT, including a Korean serotype resembling onabotulinumtoxinA and a Chinese botulinum toxin type A. Although there is some evidence to demonstrate comparable efficacy and safety of these latter products, the literature is relatively lacking in comparison to the FDA-approved products.4,5

**Upcoming Products**
Currently, there are several new BoNT formulations being studied for clinical use. RT 002 (Revance Therapeutics, Inc) is a novel injectable formulation of onabotulinumtoxinA that consists of the purified neurotoxin in combination with patented TransMTS peptides that have been shown to provide high-binding avidity for the neurotoxin, and thus the product is designed to reduce diffusion to adjacent muscles and diminish unwanted effects. With a reduced level of neurotoxin dissemination, it is theorized that a higher administration of targeted doses can be injected, which may lead to a longer duration of desired effects.6 A clinical pilot study done to establish the safety and efficacy of RT 002

### Table: US Food and Drug Administration–Approved Botulinum Neurotoxin Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>US Trade Name (Manufacturer)</th>
<th>Dermatologic Indications</th>
<th>Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbobotulinumtoxinA</td>
<td>Dysport (Ipsen Biopharmaceuticals, Inc, and Galderma Laboratories, LP)</td>
<td>Moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients aged &lt;65 years</td>
<td>Glabellar lines: a total dose of 50 U divided in 5 equal aliquots of 10 U into each of 5 sites (2 in each corrugator muscle and 1 in the procerus muscle)</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>Xeomin (Merz North America, Inc)</td>
<td>Moderate to severe glabellar lines with corrugator and/or procerus muscle activity</td>
<td>Glabellar lines: a total dose of 20 U per treatment session divided into 5 equal intramuscular injections of 4 U each (2 injections in each corrugator muscle and 1 in the procerus muscle)</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Botox (Allergan)</td>
<td>Severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients</td>
<td>Axillary hyperhidrosis: 50 U per axilla</td>
</tr>
<tr>
<td></td>
<td>Botox Cosmetic (Allergan)</td>
<td>Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients; moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients</td>
<td>Glabellar lines: 4 U/0.1 mL into each of 5 sites (2 in each corrugator muscle and 1 in the procerus muscle) for a total dose of 20 U/0.4 mL; lateral canthal lines: 4 U/0.1 mL into each of 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 U/0.6 mL (12 U per side)</td>
</tr>
<tr>
<td>RimabotulinumtoxinB</td>
<td>Myobloc (Solstice Neurosciences, Inc)</td>
<td>None</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
for treatment of moderate to severe glabellar lines evaluated 4 equally sized cohorts of 12 participants, each receiving single-dose administration of RT 002 ranging in potency equivalent to 25 U, 50 U, 75 U, and 100 U of abobotulinumtoxinA as determined by the gelatin phosphate method. It was concluded that RT 002 is both safe and efficacious with an extended duration of action, with a median duration of effect of 7 months observed in the highest dose group (dose equivalent to 100 U of abobotulinumtoxinA). Notably, 80% of all 48 participants maintained a minimum 1-point improvement in investigator-determined glabellar line severity scores at the 6-month time point and 60% achieved wrinkle scores of none or mild at 6 months posttreatment.

DWP 450 (Daewoong Pharmaceutical Co, Ltd) is derived from the wild-type Clostridium botulinum and is reported to be of higher purity than standard onabotulinumtoxinA. An initial 16-week pilot study demonstrated that 20 U of DWP 450 is noninferior and of comparable efficacy and safety to 20 U of onabotulinumtoxinA in the treatment of glabellar lines. NTC (Botulax [Hugel, Inc]) is the name of the toxin derived from the C botulinum strain CBFC26, which has already been approved in many Asian, European, and Latin American countries for the treatment of blepharospasm. This formulation has demonstrated noninferiority to onabotulinumtoxinA at equivalent 20-U doses for the treatment of moderate to severe glabellar lines in a double-blind, randomized, multicenter, phase 3 trial of 272 participants with a 16-week follow-up.

MT 10109L (Medtox Inc) is a unique product in that it is distributed as a liquid type A botulinum toxin rather than the standard freeze-dried formulation; thus, a major advantage of this product is its convenience, as it does not need reconstitution or dilution prior to administration. In a double-blind, randomized, active drug-controlled, phase 3 study of 168 participants, it was determined that MT 10109L (20 U) is comparable in efficacy to onabotulinumtoxinA (20 U) for the treatment of moderate to severe glabellar lines. No significant difference was seen between the 2 treatment groups when glabellar lines were assessed at rest at 4 and 16 weeks after treatment, but a significantly greater improvement in glabellar lines was seen at maximum frown in the MT 10109L group at the 16-week follow-up (*P = .0064).  

**Administration Techniques**

With regard to safe and effective BoNT product administration techniques, a variety of studies have provided insight into optimal practice methods. A 2015 expert consensus statement formed by an American Society for Dermatologic Surgery task force reviewed data from 42 papers and unanimously determined that for all current type A BoNT products available in the United States, a vial of BoNT reconstituted appropriately for the purpose of facial injections can be reconstituted at least 4 weeks prior to administration without contamination risk or decrease in efficacy and that multiple patients can be treated with the same vial. Although the statement was not explicit on whether or not preserved or unpreserved saline is to be used, it is considered routine practice to use preservative-containing saline to reconstitute BoNT, as it has been shown to reduce patient discomfort and is not associated with adverse effects.

**Pain Minimization**—With respect to minimizing the pain associated with BoNT injections, several studies have assessed administration techniques to minimize patient discomfort. A split-face, double-blind study of 20 participants demonstrated that the use of a 32-gauge needle has a significantly greater chance of reducing clinically significant levels of pain as compared to a 30-gauge needle when performing facial injections (*P = .04*). Overall, however, injections of the face and arms were on average only nominally and not significantly more painful with 30-gauge needles compared to 32-gauge needles.

Another technique that has been found to reduce patient discomfort is the application of cold packs prior to injection. A study of patients with chronic facial palsy observed a significant reduction in pain with the administration of a cold (3°C–5°C) gel pack for 1 minute compared to a room temperature (20°C) gel pack prior to the administration of onabotulinumtoxinA into the platysma (*P < .001*). In the matter of injection with rimabotulinumtoxinB, which has been shown to be considerably more painful to receive than its more popularly administered counterpart onabotulinumtoxinA, a split-face pilot study examined the effect of increasing the pH of rimabotulinumtoxinB to 7.5 with sodium bicarbonate from the usual pH of 5.6. Pain was reported to be considerably less in the higher pH group and no reduction of efficacy was seen over the 10-week follow-up period.

**Delivery Methods**—Several preliminary studies also have examined novel delivery techniques to identify minimally painful yet effective methods for administering BoNT. It has been reported that standard BoNT formulations are not effective as topical agents in a comparison study in which onabotulinumtoxinA injection was compared to topically applied onabotulinumtoxinA. However, a follow-up prospective study by the same authors has demonstrated efficacy of topical onabotulinumtoxinA following pretreatment with a fractional ablative CO2 laser for treatment of crow’s-feet. In this randomized, split-face,
controlled trial (N=10), participants were first pre-treated with topical lidocaine 30% before receiving a single pass of fractional ablative CO2 laser with no overlap and a pulse energy of 100 mJ. Within 60 seconds of laser treatment, participants then received either 100 U of abobotulinumtoxinA diluted in 0.1 mL of saline or simple normal saline applied topically. A clinically significant improvement in periorbital wrinkles was seen both at 1-week and 1-month posttreatment in the laser and onabotulinumtoxinA–treated group compared to the laser and topical saline–treated group (P<.02).15

Another unique administration method studied, albeit with less successful results, involves the use of iontophoresis to deliver BoNT painlessly in a transdermal fashion with the assistance of an electrical current.16 This prospective, randomized, assessor-blinded, split-axilla, controlled trial of 11 participants compared the effectiveness of administering onabotulinumtoxinA via iontophoresis to traditional injection with onabotulinumtoxinA (250 U). Iontophoresis was accomplished with a single electrode pad soaked with 250 U of onabotulinumtoxinA applied directly to the axilla and a second electrode pad soaked in 0.9% saline applied to the hand to complete the circuit. An alternating electrical current was slowly increased for 30 minutes to a maximum current of 15 mA with a voltage of 12 V. Among the 11 participants recruited, the side treated with traditional injection showed a significantly greater percentage reduction in baseline sweating at the 1-week, 1-month, and 6-month posttreatment evaluations compared to iontophoresis (84%, 76%, and 50%, respectively vs 73%, 22%, and 32%, respectively) (P<.05). Despite being less efficacious than standard injection therapy, participants reported that iontophoresis delivery was significantly less painful (P<.05).16

A high-pressure oxygen delivery device, which utilizes a powerful jet of microdroplets containing water, the drug, air, and oxygen to deliver medication onto the skin surface, also has been studied as a means of delivery of BoNT in a minimally painful manner. In this study, the device was used to assess the efficacy of transdermal delivery of BoNT via jet nebulization in the treatment of primary palmar, plantar, and axillary hyperhidrosis.17 The 20 participants included in the study were randomized to receive either a combination of lidocaine and onabotulinumtoxinA (50 U) administered through the device or lidocaine delivered through the device followed by multiple transcutaneous injections of onabotulinumtoxinA (100 U). Both treatments significantly reduced sweating compared to baseline as measured by a visual analogue scale at 3-month follow-up (P<.001), but the combination delivery of lidocaine and onabotulinumtoxinA via the device resulted in significantly less procedure-related pain and sweating (P<.001) as well as significantly greater patient satisfaction (P<.001).17

Optimizing Aesthetic Outcomes—A frequent concern of patients receiving BoNT for cosmetic purposes is a desire to avoid a “frozen” or expressionless look. As such, many clinicians have attempted a variety of techniques to achieve more natural aesthetic results. One such method is known as the multipoint and multilevel injection technique, which consists of utilizing multiple injection sites at varying depths (intramuscular, subcutaneous, or intradermal) and doses (2–6 U) depending on the degree of contractility of the targeted muscle. In a preliminary study of 223 participants using this technique with a total dose of 125 U of abobotulinumtoxinA, good and natural results were reported with perseveration of facial emotion in all participants in addition to a mean overall satisfaction rate of 6.4 of 7 on the Facial Line Treatment Satisfaction Questionnaire with the maximum satisfaction rating possible reported in 66% of cases.18 It also has been postulated that injection depth of BoNT can affect brow elevation whereupon deeper injection depths can result in inactivation of the brow depressors and allow for increased elevation of the eyebrows. This technique has been applied in attempts to correct brow height asymmetry. However, a prospective, split-face study of 23 women suggested that this method is not effective.19 Participants received 64 U of onabotulinumtoxinA via 16 injection sites in the glabella, forehead, and lateral canthal area with either all deep or all shallow injections depending on the side treated and whether brow-lift was desired. Results at 4 weeks posttreatment showed no significant difference in brow height, and it was concluded that eyebrow depressor muscles cannot be accurately targeted with deep injection into the muscle belly for correction of eyebrow height discrepancies.19 Conversely, a 5-year retrospective, nonrandomized study of 227 patients with 563 treatments utilizing a “microdroplet” technique reported success at selectively targeting the eyebrow depressors while leaving the brow elevators unaffected.20 Here, a total dose of 33 U of onabotulinumtoxinA was administered via microdrosplets of 10 to 20 μL, each with more than 60 to 100 injections into the brow, glabella, and crow’s-feet area. This method of injection resulted in a statistically significant improvement of forehead lines and brow ptosis and furrowing at follow-up between 10 and 45 days after treatment (P<.0001). Additionally, average brow height was significantly increased from 24.6 mm to 25 mm after treatment (P=.02).20

CONTINUED ON PAGE 197
CONTINUED FROM PAGE 166

**Conclusion**

The use of BoNT products for both on- and off-label cosmetic and medical indications has rapidly grown over the past 2 decades. As demonstrated in this review, a variety of promising new products and delivery techniques are being developed. Given the rise in popularity of BoNT products among both physicians and consumers, clinicians should be aware of the current data and ongoing research.

**REFERENCES**