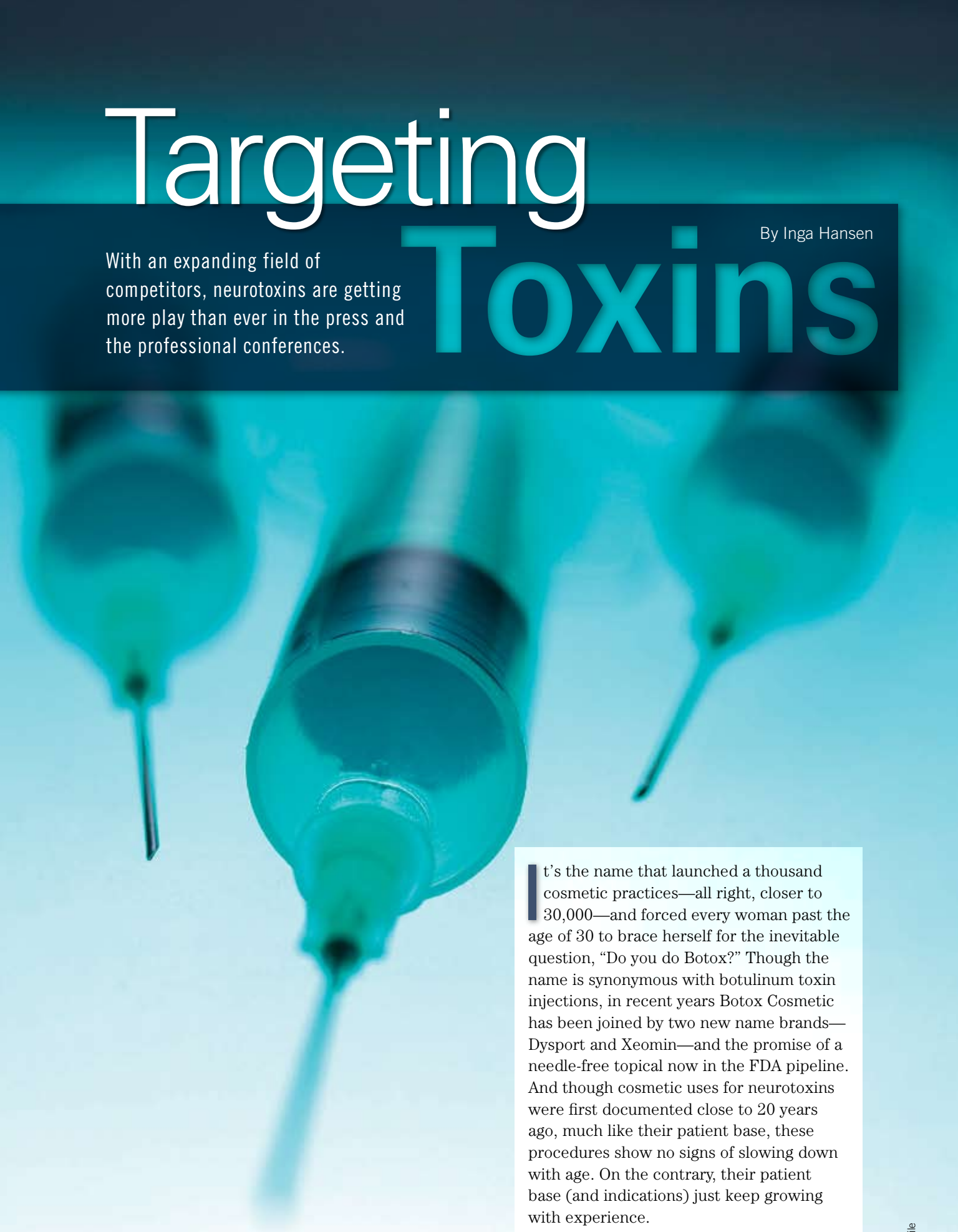
Targeting Toxins

With an expanding field of competitors, neurotoxins are getting more play than ever in the press and the professional conferences.

By Inga Hansen

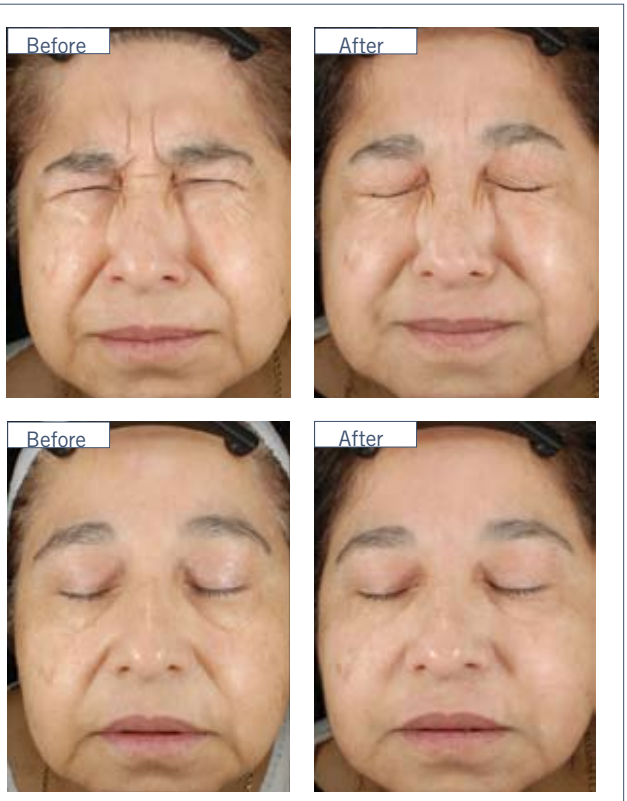


It's the name that launched a thousand cosmetic practices—all right, closer to 30,000—and forced every woman past the age of 30 to brace herself for the inevitable question, "Do you do Botox?" Though the name is synonymous with botulinum toxin injections, in recent years Botox Cosmetic has been joined by two new name brands—Dysport and Xeomin—and the promise of a needle-free topical now in the FDA pipeline. And though cosmetic uses for neurotoxins were first documented close to 20 years ago, much like their patient base, these procedures show no signs of slowing down with age. On the contrary, their patient base (and indications) just keep growing with experience.

The Effect of New Competitors

Dysport (Medicis, www.medicis.com), the first United States competitor to Botox Cosmetic (Allergan, www.botoxcosmetic.com), has been available for on-label cosmetic use for two years. With more experience under their belts, physicians are now honing in on the differences, similarities and preferred indications of the two toxins.

In terms of efficacy and patient satisfaction, one of the most debated topics when comparing the use of Dysport to Botox Cosmetic has been dosing and conversion rates. According to their respective labeling instructions, the conversion of Dysport to Botox Cosmetic is 2.5:1. But clinical experience has suggested to many that the recommended conversion is not adequate for optimal correction. Vic Narurkar, MD, associate clinical professor of dermatology at UC Davis Medical School and founder of the Bay Area Laser Institute (www.bayarealaserdr.com), performed a study—which was presented at the 2010 American Society for Dermatologic Surgery Meeting in Chicago—with 30 of his neurotoxin patients to determine optimal conversion rates. He limited the subjects to patients who had used Botox Cosmetic before, "so we knew exactly how many units they needed to achieve an optimal cosmetic outcome," he says. He further restricted the study to patients who had not received a Botox Cosmetic treatment in at least six months. Dr. Narurkar then randomized the patients to getting either Dysport or Botox injections at different conversion ratios of 2.5:1, 3:1 or 4:1, "because if you look at the literature [the ratios] are all over the place," he says.



This patient—pictured at rest and at full expression—received Botox Cosmetic to the glabella and periorbital area and Juvederm Ultra Plus XC in the marionette lines and nasolabial folds.

For the crow's feet, patients received Botox Cosmetic on one side and Dysport on the other, based on the three conversion rates. "We found out that the range was between 3:1 and 4:1," says Dr. Narurkar. "For the glabella, we randomized patients to getting either Botox or Dysport. We found again that the conversion range is anywhere from 3:1 to 4:1, but the brow lifting was much more consistent in the Botox group than the Dysport group."

Shortly after Dysport's release, physicians began noticing that one of the key differences between the two neurotoxins is that Dysport appears to have a more diffuse spread pattern than Botox. Two years later, this difference continues to be confirmed in clinical use and dictates both patient selection and indications. Joseph Eviatar, MD, an oculofacial plastic and reconstructive surgeon with Chelsea Eye & Cosmetic Surgery Associates (www.chelseaeye.com), prefers Dysport for male patients with high foreheads and multiple lines, "where you want to relax the muscle and reduce the lines, but not freeze them," he says. "Because Dysport has a wider spread, you can achieve a softer look on these patients." He also notes that, due to the wider spread, injection points are slightly different with Dysport versus Botox.

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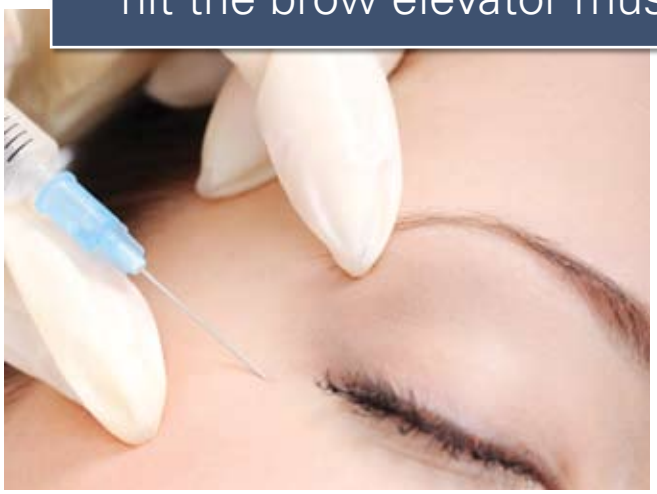

Top: Photo courtesy of Vic Narurkar, MD; Bottom: © Istockphoto.com

smoother look than Botox and ends up covering a larger area for the same number of injections," notes dermatologist Joel Schlessinger, MD, of Lovely Skin (www.lovelyskin.com).

When treating women with smaller foreheads who desire a slight brow lift and reduction in the furrow of the brow, Dr. Eviatar chooses Botox Cosmetic. "Dysport is going to give you too much spread [in these patients], and you won't be able to lift the brow as much, because you're going to hit the brow elevator muscle."

Dr. Narurkar concurs, noting, "I do not use Dysport for brow lifting, based the results of our study." He did find, however, that when using a conversion rate of 3:1 to 4:1 "in the crow's feet area, results are quite equivalent."

At the 2010 ASDS meeting in Chicago, Monika Kiripolsky, MD, of True Beauty Skin & Laser (www.trubeautymd.com), presented a study that suggested a faster onset of action for Dysport versus Botox Cosmetic. The practice followed 1,000 patients—75% were treated with onabotulinumtoxinA (Botox) and 25% with abobotulinumtoxinA (Dysport)—in two four-month phases. The patients were asked to complete a questionnaire covering onset of action, duration of results and patient satisfaction. Phase I used a 2.5:1 conversion rate. Phase II used a 3:1 conversion rate. Based on the questionnaires, the duration of effect for Dysport was only 6 weeks in the 2.5:1 conversion rate group versus 10 weeks in the 3:1 conversion rate group. In terms of overall patient satisfaction, 50% of patients preferred Botox Cosmetic, 25% preferred Dysport and 25% had no preference. The Dysport patients also reported a faster onset of action.

In Dr. Narurkar's study, however, "we did not see that at all, and what was beautiful about our study is both products were made up at the same time, so it was fresh product," he says. "We looked at photos at 0 hours, 24 hours, 48 hours, one week, four weeks and three months, and the person looking at the images did not know which was Botox and which was Dysport." His reviewers saw no difference in onset of action or duration of results. "Our conclusions were that you cannot do a simple conversion from Botox to Dysport to achieve a consistent cosmetic outcome, they each have unique units," says Dr. Narurkar. "We also found that brow lifting was more consistent with Botox, and there was absolutely no difference in onset or longevity."

Enter Xeomin

Though Xeomin (Merz Pharmaceutical, www.merzusa.com) has not yet received FDA approval for cosmetic indications, its August 2010 approval for the treatment of dystonia and blepharospasm has brought the botulinum toxin to market in the United States. Unlike Botox Cosmetic and Dysport, Xeomin is a pure protein and requires no refrigeration. But that seems to be where the dissimilarities end. "Xeomin is very similar to Botox in that the unit measurement is 1:1," says Dr. Eviatar. "It was designed to be a swap-out product."

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According to Dr. Eviatar, onset and duration of action also appear to be very similar, though there is still a lack of data due to its recent introduction. "The potential advantage of Xeomin over Botox is theoretical at this point," he says. Because Xeomin is a naked polypeptide, "potentially the body will not recognize it and dissolve it, so patients who have developed resistance to Botox over the years, may not experience resistance to Xeomin," continues Dr. Eviatar. "With the way Botox is manufactured today, it's probably less than 1% of patients who develop resistance or fail to respond to the product over time. Theoretically, there should be even less with Xeomin."

Where Dysport has consistently shown a more diffuse spread pattern than Botox, "This doesn't seem to be the case in studies comparing Botox to Xeomin," says Dr. Schlessinger.

Because Xeomin requires no refrigeration, it does offer some benefits to physicians, especially those who do a small volume of neurotoxin treatments. "From the patient's point of view, there's no big difference that we can determine," says Dr. Eviatar.

He generally chooses Xeomin for patients who've "had Botox and maybe aren't thrilled with the result or feel like it didn't last as long as they'd like," says Dr. Eviatar. "Generally, I have a low threshold for switching my patients over to Xeomin, it gives them another product to try. That said, I am generally of the mind, if it ain't broke, don't fix it. And most of our patients who use Botox get really great results and are very happy with the product. In addition, we know exactly, over time, how to dose them in which area. So, we don't want to change something that's working really well, particularly since I use Botox in small units here and there to gently shape the face. It's quite a nuanced approach"

The success and exceptional safety profile of Botox Cosmetic—rather than any shortcomings on the part of new entrees—appears to be what's driving most doctors to remain with the trusted brand. "Botox remains the workhorse of my practice. Nothing else can replace it," says Dr. Narurkar. "It is the one thing that consistently delivers. During the recession, this is also the one area of my practice that actually grew. Patients get used to how they look with it, and it's very hard to give up. That's part of why I'm so hesitant to switch. When patients are so happy with a product, unless there is a really compelling reason to change, you don't change."

One compelling reason for change that many doctors were looking forward to with the introduction of new competitors in the neurotoxin market has yet to occur. That is: price breaks that can be passed on to attract new patients. "It takes more units of Dysport to treat the same areas as Botox, and once you take that into account, there is no price difference, which surprised me," says Linda Coffey, MD, founder of San Antonio Dermatology (www.sadermatologist.com). "We were all hoping that it would come in cheaper and we'd have real competition. Maybe we will see that with Xeomin."

Short of a significant decrease in price or increase in duration of results, it is likely that new competitors will continue to fill niche markets in most cosmetic practices. There is, however, another neurotoxin option in the FDA pipeline that has the potential to attract a brand new patient base, topical neurotoxin RT001 from Revance Therapeutics (www.revance.com).

Needle-Free Neurotoxins

The first of the anxiously awaited, topically applied neurotoxins, RT001 is currently in Phase III clinical trials. The product—which will be available by prescription only and is applied by the physician—includes both botulinum toxin type A and a peptide carrier to help the toxin penetrate the skin. "I'm very excited about it, because we have a lot of needle-adverse patients, so this will bring people into the practice who [might] not have come in before," says Dr. Narurkar. "I don't think it will adversely affect our injectable practice, I think it will actually expand it. But [the product] does have to be as good or better than the current injectables. It won't be successful just because it's needleless."

The results of two Phase II clinical trials on RT001 were presented at this year's annual meeting of the ASDS in Chicago. Fredric Brandt, MD, a dermatologist in private practice in New York and Miami, acted as the principal investigator of the study. Gary Monheit, MD, clinical associate professor at the University of Alabama, presented the results, which showed that RT001 was well tolerated and demonstrated statistically significant efficacy versus controls. In both studies, adverse events were rated by investigators as generally mild or moderate, and transient. According to Dr. Monheit, there was also no evidence of spread or diffusion away from the target muscle observed.

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The first study included 90 subjects whose results were both self-rated and recorded by an investigator following validated wrinkle-severity scales. According to a company release, "To be a responder, each subject had to demonstrate a ≥2-point improvement on both sides of the face as graded by the investigator's assessment and the patient's self-assessment. RT001 met the primary endpoint and all secondary endpoints with $p \leq 0.0001$."

The second study had 180 subjects and was designed to compare the individual components of RT001—botulinum toxin type A, the proprietary peptide carrier and the

vehicle. According to Dr. Monheit, RT001 met the primary endpoint of ≥2-point improvement in lateral canthal line severity on both sides of the face as measured by the investigator in patients who received all the components. According to the company, "RT001 also met the more stringent composite endpoint of ≥2-point improvement on both the investigator assessment and the patient's self assessment compared to controls ($p<0.0001$)," suggesting that the peptide carrier is necessary for the topically applied botulinum toxin to achieve positive results. At the time we went to print, the company was in discussions with the FDA to move on to Phase III trials.

"When I first heard about topical neurotoxins, I thought, this is just silly, it's not going to work," says Dr. Eviatar. "But, if you can get the effectiveness with a topical neurotoxin, they may fit in nicely. With an injection, you can be very precise in placement and concentration. Obviously, with a topical I think you will have less control. My gut feeling is that the topical will be for very straightforward correction—if you're just softening the frown muscle and so forth—but for more nuanced corrections, you'll have less ability to control what you're doing."

The benefit to the patient, of course, is that she will not have to endure uncomfortable injections and needle pricks. The benefit to doctors is less clear. "With the injectable toxins, it's a relatively rapid procedure," says Dr. Narurkar. "So my biggest question is how will physicians embrace a topical in terms of treatment time."

Expanding Indications

In recent years, injectable neurotoxins have moved from the glabella down to the mid-face and even onto the jaw line and neck to tighten and sculpt the face while banishing lines in a bevy of locations. Advanced injectors are using neurotoxins for periorbital rejuvenation, around the orbicularis oris to reduce lip lines and at the platysmal bands to diminish neck lines. One of the latest techniques, known as mesoBotox, involves injecting very dilute doses all over the face for skin texture rejuvenation and firming.

"More and more we are using Botox for off-label, pan-facial rejuvenation with a combination of Botox, fillers and devices," says Dr. Narurkar. "We're also very excited about the potential of mesoBotox—injecting very dilute doses in the cheeks for very fine lines—this is an untapped area for us. We're also looking at lower third facial applications, expanded for use in the depressor anguli oris and the mentalis. These are all very exciting avenues."

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Dr. Coffey notes that, while neurotoxins offer both efficacy and safety for patients, "there is an age range for these products. For most women, it is in their 30s to their 60s," she says. "Once you get into the 80s, these products just don't work. There are also some women in their 20s who have very deep lines in the glabella region, and neurotoxins are very effective for them, but for most women [the ideal time for treatment] is in their 30s to their 60s."

The continued demand from patients and ongoing innovations in clinical use signal that the popularity of neurotoxins will continue to grow for some time. And most believe that as new competitors seek to share the market, public awareness of these procedures will only increase. Dr. Eviatar, for one, believes that new formulations will need to offer some noteworthy new benefits to truly cut into the Botox stronghold. "The things patients are really concerned about are: how long does it last, how much does it cost and, maybe to a lesser extent, how fast does it work?" he says. "If you can get something to work in a day and last up to four or five months—patients would like that. If it's also cheaper, they would really like that. In these three categories, I don't think we have a home run yet with any of these products."