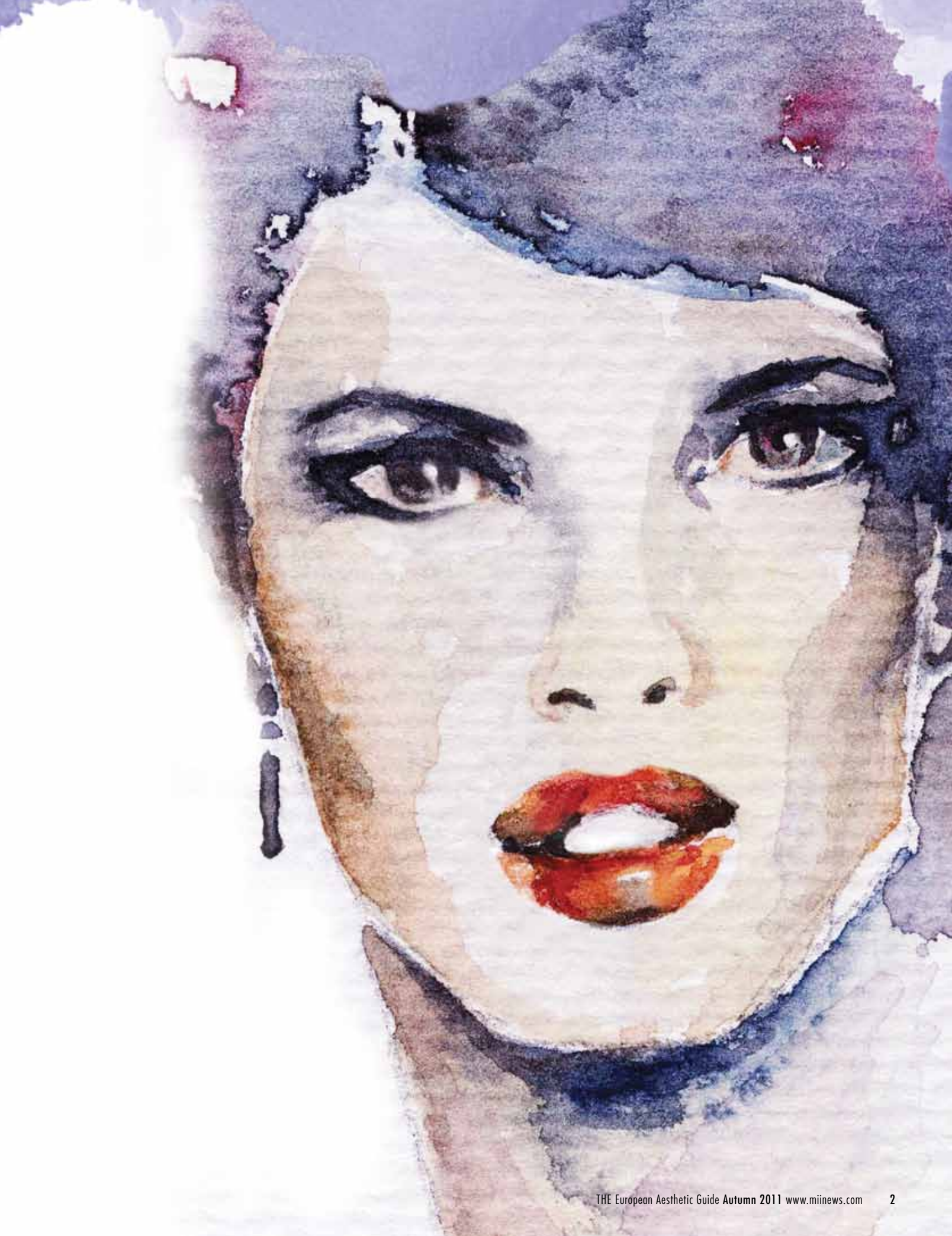




RESEARCHER PREDICTS FUTURE GENERATIONS OF **Neurotoxins**

By Andy Pickett, Ph.D., B.Sc., Founder and Director, Toxin Science Limited

First generation botulinum toxin type A (BoNT-A) products – Dysport® from Ipsen (Paris, France) and BOTOX® from Allergan (Irvine, California, U.S.) – have been available for therapeutic uses for over 20 years. During this time, their applications have widened, mostly through off-label applications by pioneering clinicians. In Europe, these first generation products were transformed for aesthetic use. Galderma (Lausanne, Switzerland) and Allergan presented lower dose formulations of Dysport and BOTOX in the form of Azzalure and Vistabel, respectively.



Both Dysport and BOTOX are toxin complexes, where the active neurotoxin component is associated with other proteins produced naturally by the bacteria that make the BoNT-A. Manufacturers of the different product families highly purify the toxin complexes before preparing the product in vials, but use divergent production procedures.

A second generation of therapeutic BoNT products has been available for over five years. Originally called NT201, Xeomin®, from Merz (Frankfurt, Germany), was first made available in Germany, and is now available throughout Europe, the U.S., Canada and other countries. The product is manufactured using additional stages to remove the other proteins of the BoNT-A complex, yielding a product that is “free from complexing proteins.” This is different than saying the product is pure; there is evidence, as shown by Merz in podium presentations, that there are other (toxin-related) components in their product, but no scientific literature has yet been published containing these data. The aesthetic low dose version of Xeomin (Bocouture®) is just becoming available.

The big question now is: Where do we go from here with neurotoxin products? Everyone wants to know what the next generations of BoNT products are likely to look like and where they will come from.

Another second generation BoNT-A product is PurTox®, produced originally by Mentor (Santa Barbara, Calif.), and taken over by Johnson and Johnson (Skillman, New Jersey, U.S.) in early 2009. While there is much reported on the Internet about PurTox, it has been in clinical trials for several years with no sign of the product being licensed by the FDA. According to podium presentations, clinicians testing the product have indicated an ongoing series of long-term assessments (up to three years) of patients being treated.

The big question now is: Where do we go from here with neurotoxin products? Everyone wants to know what the next generations of BoNT products are likely to look like and where they will come from. Not surprisingly, work is already underway and the answers fall into two distinct categories – applying toxins with needles and without needles.

A seemingly obvious improvement to BoNT treatments would be to consider different techniques of administering the products. Some patients do not like injections; therefore, an alternative method would be topical application. Consequently, two topical products are currently under investigation.

The first product, RT001 from Revance Therapeutics, Inc. (Newark, California, U.S.), uses a topical agent that allows the BoNT to penetrate the skin. This technology, called Trans MTS™, first coats the BoNT molecules (termed “assembly”) then carries them through the dermal layers to the main site of action at the neuromuscular junction, where the nerve meets the muscle fiber. The product is formulated at the point of use by the clinician and consists of a purified BoNT neurotoxin with the carrier.

Details of the BoNT product itself have not been divulged except that it is pure BoNT-A neurotoxin. Nonetheless, the company often publicly shares the progress of the ongoing trials through their main clinical investigators with highly promising results in the treatment of lateral canthal lines (crow’s feet)¹. Other limited, but successful tests have been reported for the treatment of hyperhidrosis², but this does not seem to be their main target indication as no new data have been reported for some time.

After the treatment is applied by the clinician, the patient has to wait for 30 minutes before the product is removed. This may cause simple logistical issues when treating several patients in turn.

A second company, Transdermal Corporation (Birmingham, Michigan, U.S.), is also developing a topical agent based on Trans Ionic Nanoparticle

Technology (InPar™). This technology consists of micelles (surfactants and protein solubilizers), coated with lipid molecules that entrap the active component with no changes in chemical composition – the particles are one to ten nanometers in size; smaller than skin pores.

This drug delivery technology is being tested for administering lidocaine, benzoyl peroxide for acne, hyaluronic acid dermal fillers and BoNT-A. One cosmetic cream is already available under the label DERMAL FX. The technology is currently in trials with BoNT-A for glabellar lines, crow's feet and hyperhidrosis. To date, data from the clinical results are scarce – one paper has been published (giving the brand name as CosmeTox)³ – but a comprehensive review of what has been achieved so far is available on the Internet as a slide presentation⁴ by their clinical consultant, Mark Nestor, M.D., Ph.D., dermatologist and director of the Center for Cosmetic Enhancement and the Center for Clinical and Cosmetic Research (Aventura, Florida, U.S.).

Other topical BoNT-A preparations and proposed products have surfaced. For example, Refitox® botulinum lotion⁵, manufactured in China by DPS Technology Development Ltd., and sold over the Internet, is reported to contain a, "botulinum toxin type A metabolite gene protein component," (in other words, BoNT-A), together with a vitamin, hyaluronic acid, rose extract and aloe extract. However, whether this lotion has any effect or not remains to be verified.

Patent literature is another rich source of potential topical presentations for BoNT products. For example, a patent application, published in April 2008 by the University of Massachusetts, describes the preparation of "botulinum nanoemulsions," prepared by different methods and having a particle size upwards of 10 nanometers. According to the application, this type of product "may be self-administered in the privacy of one's home, without medical supervision." Whether such a possibility is achievable will be entirely dependent upon the regulators.

From these examples, it is obvious that topical application of BoNT is actively being worked on

and looks like it is here to stay. The benefits of non-injection are clear, but the actual regulatory process, hurdles and feasibility remain to be fully tested. In addition, logistical aspects (waiting room times) and handling by the patients themselves (if this is permitted) will need to be carefully examined and controlled.

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Another method of allowing BoNT-A to cross the skin barriers without needles is with the use of iontophoresis, otherwise known as Electromotive Drug Administration. Using a special machine that applies a small electric charge to deliver the product, this technique is non-invasive and propels the active component through the dermal layers.

Iontophoresis has been used to effectively treat hyperhidrosis using nothing more than water as the propelled product. Instead of multiple, often painful injections in the hands (for palmar hyperhidrosis), the patient undergoes iontophoresis for about five minutes per site, treating several sites per hand. A few limited studies have been carried out very successfully over the last seven years in conjunction with BoNT-A. A 70% reduction in sweating has been seen for up to three months.⁶

Iontophoresis units are small, portable and inexpensive – even self-contained and powered patches are available. Significantly, more clinical studies are needed for this exciting approach and clinicians are often specifically interested in treating hyperhidrosis, when the technique is outlined.

Of interest with both transdermal and iontophoretic delivery systems for BoNT-A is that, in theory, the size of the BoNT-A molecule is too large (150 kDa) to penetrate the skin, especially given the five different layers that make up the epidermal barrier. Oxygen, nitrogen and carbon

dioxide can penetrate the epidermis in small amounts and water can be absorbed, but an effective barrier to water evaporation is also formed. Since the stratum corneum contains high amounts of lipids (over 50%), the passive action of a topical BoNT-A has been described initially as "lipid rafting," which allows the lipid-covered BoNT-A molecule to effectively slide through the upper lipid layers, followed by a more active transportation into the dermis. This does not however, explain the beneficial action of iontophoresis. Clearly, more work is needed to explain the detail of these phenomena.

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While eliminating needles in the delivery of neurotoxins will be revolutionary, advancing injection methods is another progressive step. An alternative method of toxin administration could be through the use of liquid preparations, perhaps in pre-filled syringes or similar administration devices, thereby effectively removing the reconstitution step for the clinician. Since dermal fillers are routinely supplied in pre-filled syringes, it would seem natural to do the same with BoNT products.

Without doubt, the concept of a liquid formulation for BoNT products has been in existence for many years. BoNT type B has been available as a liquid formulation in a vial since license approval in December 2000. Over the last decade, there have been many reports that this product hurts upon injection, likely due to the acidic pH of the solution. Therefore, a formulation that is not painful is key to a successful future liquid product. Shelf-life stability will also be essential; a

subject that has been effectively dealt with by all the other freeze-dried or vacuum-dried products with their stable formulations.

Patent applications filed by Allergan, Ipsen, Solstice Neurosciences (Louisville, Kentucky, U.S.) and Medytox (Seoul, Korea), together with other individual clinicians and scientists, contain numerous references to liquid formulations. These formulations all have different stabilizers and components, including omission of the Human Serum Albumin now used in all products.⁷ As such, they should be considered next-generation formulations and will be made available as soon as stability and presentation issues are determined by the manufacturers. Also, these new formulations will have to show that they are equivalent to current marketed products.

Additionally, other devices are beginning to appear that are designed to make BoNT injections easier. One such example is the neurotoxin automatic injector called Talent™ BT from Primequal (Gland, Switzerland), recently shown at the *International Master Course on Aging Skin (IMCAS)* in Paris, France, January 2011. This injection pen is intended to provide automated, consistent injections of precise volumes of reconstituted product; however, it is unclear whether it offers any real advantages to an experienced injector. Furthermore, the device produces an audible 'click' each time the trigger is pressed which could be somewhat disconcerting to a patient.

While physicians and patients eagerly await these third generation products, perhaps more remarkable is that work on fourth generation BoNT products is already well advanced. These products are modified toxins – BoNT molecules that have been changed in some way to either improve efficacy or retarget the activity to other functions in the body.

Already, a new molecule (AGN-214868), developed by Syntaxin in conjunction with Allergan, is in clinical trials. This modified BoNT is being viewed as a new therapeutic protein, rather than a toxin, and is being tested in, for example, post-herpetic neuralgia and idiopathic

overactive bladder. No other specific details of the molecule have been published.

Significantly, Revance Therapeutics is also developing new, fourth generation BoNT products. The first, termed RT002 is said to have a, "favorable duration of effect and safety profile," according to the manufacturer. In 2009 Medicis invested heavily in this new technology and the first publication about this molecule has just appeared.⁸

There are many other examples of BoNT molecules being modified to achieve different activities and/or different targets. These were recently reviewed in detail.⁷ Perhaps the most interesting – from an aesthetic standpoint – are related to modifying the duration of action. A longer duration BoNT product would be a valuable addition to aesthetic treatments. Future developments in BoNT science will help direct the changes needed to achieve these goals. ■

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