AbobotulinumtoxinA: A 25-Year History

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Abstract

During the late 1960s and early 1970s, Alan Scott showed that intramuscular injections of botulinum toxin (BoNT) corrected nonaccommodative strabismus without resorting to surgery. The UK doctors who trained with Scott soon realized the significant potential offered by BoNT type A as a therapeutic option for several difficult-to-treat diseases. This led to a collaboration between these pioneering clinicians and the Centre for Applied Microbiology and Research at Porton Down, United Kingdom, and, in turn, to the development and commercialization of abobotulinumtoxinA as Dysport (Dystonia/Porton Down; Ipsen Biopharm Ltd., Wrexham, UK). Dysport was approved in Europe for the treatment of specific dystonias in December 1990 and now has marketing authorizations in 75 countries. Since then, the use of BoNT in therapeutic and aesthetic indications has grown year-on-year, and continues to expand well beyond Scott’s initial aim. For example, ongoing trials are assessing potential new indications for BoNT-A, including acne and psoriasis. Furthermore, a growing number of other BoNT products, often termed “biosimilars,” together with innovative formulations of well-established BoNT types, are likely to reach the market over the next few years. This review focuses on the history of Dysport to mark the 25th anniversary of its first launch in the United Kingdom.

During the late 1960s and early 1970s, Alan Scott, based at the Smith-Kettlewell Institute of Visual Sciences, now known as the Smith-Kettlewell Eye Research Institute (SKERI), San Francisco, used intramuscular injections of botulinum toxin (BoNT) to weaken ocular muscles in monkeys as a potential alternative to surgical correction of nonaccommodative strabismus. Since then, the use of BoNT in therapeutic and aesthetic indications has grown year-on-year and expanded well beyond Scott’s initial aim. BoNT is, for example, often the treatment of choice for spasticity related to stroke, multiple sclerosis, head and spinal cord trauma, cerebral palsy, and several types of motor neuron disease. BoNT is also a therapeutic mainstay for other conditions, such as axillary hyperhidrosis, chronic migraine, and neurogenic detrusor overactivity. The range of potential therapeutic uses continues to expand, with recent clinical studies suggesting that BoNT may be effective for some cases of psoriasis, acne, and lateral patellofemoral overload syndrome, although these are currently investigative clinical studies and BoNT is unlicensed for these indications.

In addition, BoNT has found numerous aesthetic uses, including the treatment of forehead wrinkles and other...
facial hyperkinetic movements, as well as glabellar, peri-orbital, and perioral lines. According to the American Society of Plastic Surgeons, 15.9 million aesthetic procedures were performed in the USA during 2015. BoNT injections were the most common of these. Indeed, the 6.8 million BoNT injections performed during 2015 was the highest number on record.

This review focuses on the history of one of the major BoNT products, abobotulinumtoxinA (ABO; Dysport; Ipsen Biopharm Ltd., Wrexham, UK), to mark the 25th anniversary of the first launch in the United Kingdom. Dysport has become a widely used BoNT product, with marketing authorizations for various conditions in 75 countries.

FROM SAUSAGES TO STRABISMUS

Cases of botulism associated with poor food storage—such as ham kept in barrels of brine, poorly dried and stored herring, and lightly smoked fish or ham in poorly heated smoking chambers—have probably occurred since antiquity. Indeed, some historical cases of suspected Atropa belladonna poisoning were probably caused by foodborne botulism. In 1793, for example, 13 people contracted botulism in Wildbad, a village in southwest Germany; 6 of them died. All of the victims showed mydriasis (dilation of the pupils) and, therefore, physicians initially blamed A. belladonna. The name belladonna ("beautiful woman"), incidentally, reflects the use of A. belladonna eye-drops by women during the Italian Renaissance to enhance their ocular appearance by inducing mydriasis.

The Wildbad outbreak was later traced to a dish of cooked pork stomach filled with blood sausage. During the 19th century, doctors recognized that the Wildbad outbreak was not an isolated incident. Indeed, poor hygiene associated with the economic depression in the wake of the Napoleonic War (1795-1813) probably contributed to numerous outbreaks of fatal food poisoning, including several cases of botulism from smoked blood sausages.

In July 1802, for example, the government in Stuttgart warned the public about eating smoked blood sausages. Justinus Andreas Christian Kerner, a German physician, poet, and medical writer, published the first case studies on botulinum toxicity in 1817 and 1820. Kerner was interested in these cases of food poisoning and death through his work as a medical officer in Wildbad in 1811. He identified a “fat poison” or “fatty acid,” which was later identified as BoNT, as the culprit. He administered this “fat poison,” extracted from “sour” sausages, to a variety of experimental animals, including birds, cats, rabbits, frogs, flies, locusts, and snails. In addition, Kerner tested the “fat poison” on himself, noting that a few drops on the tongue caused marked drying of the palate and pharynx. In his 1822 monograph, Kerner suggested that the “fat poison” from sour sausages interrupted nerve conduction, reduced pathological hyperexcitability, and caused clinical botulism.

In 1869, the German physician John Muller coined the term “botulism,” from “botulus,” the Latin for sausage.

The Discovery of Clostridium Botulinum

The exact reason for the occurrence of the toxin remained elusive until 1895, when the microbiologist Emile Pierre-Marie van Ermengem, working at the University of Ghent, isolated an anaerobic microorganism from contaminated pickled and smoked ham. The ham had been eaten by victims of a botulism outbreak traced to a funeral in Ellezelles, a village in Belgium. Van Ermengem called the microorganism Bacillus botulinus, but it wasn’t until the German physician Ludwig Brieger coined the term “toxin” in 1890 that this became associated with Kerner and van Ermengem’s findings.

In 1917, the Committee of the Society of American Bacteriologists on Characterization and Classification of Bacterial Types differentiated Bacillus and Clostridium into “2 distinct series.” Bacillus are aerobic microorganisms, the committee suggested. In contrast, Clostridium are anaerobic, rod-shaped bacteria. Ida Bengtson (see below) noted that, as well as being anaerobes, the taxonomy of Clostridium was especially apt for the strains responsible for botulism. C. botulinum are spindle- or tadpole-shaped, or ellipsoidal, which helps to discriminate Clostridium species from other anaerobic genera. (Clostridium derives from kloster, the Greek for spindle.)

Despite the fatalities, van Ermengem found that C. botulinum was not generally pathogenic, and confirmed Kerner’s deduction that a toxin was responsible for clinical botulism. Initially, microbiologists believed food contaminated with toxin produced by C. botulinum caused all adult cases of botulism. However, in California in 1931, an infant was suspected as having contracted botulism. Although clinicians considered foodborne botulism during the differential diagnosis, the patient was discharged with a diagnosis of encephalitis. Researchers who reviewed the case in 1979, “unequivocally diagnosed” that this was the first recorded case of infant botulism. This case probably followed ingestion of contaminated milk products, although researchers discovered C. botulinum spores in the intestines of babies in the 1970s. Meanwhile, in 1945, Ivan Clifford Hall at Columbia University, New York, isolated C. botulinum type A (BoNT-A) from 2 lacerated wounds free of serious infection and type B from a severe compound fracture. These identifications of infant and wound botulism resulted in a growing recognition of routes of transmission other than food.

Microbiologists also increasingly realized that C. botulinum was a heterogeneous species. In a 1910 paper, J. Leuchs, a microbiologist at the Royal Institute of Infectious Diseases in Berlin, recognized that the strain of C. botulinum that resulted in a 1904 outbreak of botulism caused by canned white beans differed from that which had been found in the Ellezelles ham, and that the toxins were serologically
distinct. In 1919, Georgina Burke, at Stanford University, examined 12 strains of *C. botulinum*, including 5 from outbreaks of poisoning from home-canned vegetables and fruits. Based on toxin-antitoxin reactions, Burke identified 2 strains, which she consequently designated A and B. In 1924, Bengtson reported the identification of type C from a strain isolated from the larvae of the green bottle fly *Lucilia caesar*. The strain had been used experimentally to, for example, induce avian botulism (“limberneck”) in chickens.

Microbiologists now recognize 4 phenotypic groups and genotypic lineages of *C. botulinum* (designated groups I-IV) and that BoNT exists in 7 distinct antigenic types (designated serotypes A-G). These phenotypic groups produce different BoNTs: Group I produces A, B, and F; Group II produces B, E, and F; Group III produces C and D; and Group IV produces G. The closely related bacteria *C. baratti* and *C. butyricum* express BoNT types F and E, respectively. There are currently known to be at least 45 different subtypes of the various serotypes. BoNT-A, -B, -E, and -F are responsible for diseases in humans. BoNT types C and D are typically more relevant to botulism in poultry and other animals. Indeed, BoNT type D effectively induces skeletal muscle paralysis in mice, but shows little electrophysiological activity in human muscle.

In 1928, researchers at the University of California reported that they had chemically purified BoNT-A using selective adsorption on colloidal aluminium hydroxide, elution with secondary ammonium phosphate, dialysis, and evaporation. This process precipitated a stable, light brown, dry powder form of BoNT-A that was readily soluble in water. In 1946, Carl Lamanna et al at Fort Detrick reported that they had chemically purified BoNT-A using selective adsorption on colloidal aluminium hydroxide, elution with secondary ammonium phosphate, dialysis, and evaporation. This process precipitated a stable, light brown, dry powder form of BoNT-A that was readily soluble in water. This paved the way for therapeutic applications of BoNT, beginning with strabismus.

**THERAPEUTIC USES OF BoNT**

Kerner was the first to fully describe the characteristic neuromuscular symptoms of botulism, which include diplopia (usually the first symptom), vomiting, intestinal spasms, mydriasis, ptosis, dysphagia, and respiratory failure. Many years before the discovery of *C. botulinum*, these clinical presentations inspired suggestions that botulism might have therapeutic potential. Kerner, for instance, presciently proposed that botulinum toxin could be used therapeutically to lower sympathetic nervous system activity associated with movement disorders (eg, chorea minor) and hypersecretion of body fluids, ulcers from malignant diseases, delusions, rabies, plague, and consumption associated with lung tuberculosis and yellow fever. Nevertheless, such suggestions remained speculation for more than 150 years, until the landmark studies performed by Alan Scott, an ophthalmologist at SKERI in San Francisco.

Several researchers before Scott had proposed that neurotoxins could correct strabismus by relaxing periocular muscles. The ophthalmologist Conrad Berens seems to have been the first to assess whether “neurotoxins” could improve strabismus by injecting alcohol into human extraocular muscles. However, the effects on the muscles were generally inadequate, but occasionally caused total, permanent paralysis. Several other researchers tried alternative toxins, although their results do not seem to have been published and are cited as personal communications by Scott. This lack of publication might reflect the fact that the pharmacodynamics and toxicity of many chemical agents were inappropriate, and that injecting specific muscles proved problematic.

During the 1960s, Scott took up the challenge of identifying a substance to inject into the hyperactive muscles that cause strabismus. Scott tried several substances in monkeys with surgically induced strabismus. Although these pre-BoNT studies were unsuccessful, Scott observed that ketamine produced surgical levels of anesthesia while preserving an active electromyograph signal recorded by an electrode at the tip of the injection needle. This observation facilitated the evaluation of neurotoxic agents after injection into specific extraocular muscles.

The ophthalmologist Alfred Maumenee suggested that Scott should try BoNT. Maumenee had worked on the toxin after the Second World War at Camp Detrick. Scott contacted Edward Schantz at the University of Wisconsin, who supplied highly purified crystalline BoNT-A. Since 1946. He also considered saxitoxin produced by the dinoflagellate *Gonyaulax catenella*, which is responsible for certain outbreaks of seafood poisoning. Both toxins cause flaccid paralysis of skeletal muscle. BoNT-A, however, appeared to be the toxin of choice as survivors of botulism food poisoning were paralyzed for many weeks, emphasizing the long duration of effect that was possible. In contrast, survivors of saxitoxin poisoning recovered in a few days.

In 1973, Scott published the results of his use of injections of BoNT-A to weaken ocular muscles in rhesus monkeys using a model of “induced strabismus.” The long-term benefits of BoNT-A were apparent even from these initial studies. Injecting BoNT-A into the horizontal rectus muscles produced paresis that, depending on the dose, lasted for between 2 weeks and 8 months. In his landmark paper, Scott suggested that BoNT-A might “replace or augment existing methods of surgical correction of strabismus.” In addition, he noted that BoNT-A might counter lid retraction in endocrine exophthalmos, reduce blepharospasm, and influence skeletal muscle groups.

Six years later, during the American Academy of Ophthalmology meeting in San Francisco in November 1979, and also in a paper published in *Ophthalmology*, Scott reported results using BoNT-A to correct strabismus in humans based on injection of 67 doses of toxin into 19 patients. Maximum paralysis occurred 4 to 5 days following the injection, then showed a dose-dependent decline. A further paper followed that analyzed the results from 132...
doses of BoNT-A injected into 42 patients with strabismus. The effect on horizontal strabismus was uniformly beneficial and lasted for up to 411 days. 30 Scott commercialized BoNT-A as “Oculinum” through his company Oculinum, Inc. (Berkeley, CA). 35 The United States Food and Drug Administration (FDA), approved the BoNT-A product for blepharospasm and strabismus in 1989. 36 Allergan (Irvine, CA) purchased Oculinum soon after it was licensed in the United States, and then rebranded it as Botox. 37

In the meantime, clinicians from around the world visited SKERI to learn how to inject the periorcular muscles, and left with samples of BoNT-A. In 1981, for example, John Lee, who was to become president of the Royal College of Ophthalmologists in the United Kingdom, visited SKERI and received samples of the Schantz–Scott BoNT-A. 38 Lee was a member of a group from Moorfields Eye Hospital, London, who subsequently injected BoNT-A into the lateral or medial rectus muscle of 85 adults with horizontal concomitant strabismus. BoNT-A reduced the ocular deviation by an average of 60% independently of the extent of the strabismus and irrespective of whether the patient had previously undergone surgery. 39 In turn, clinicians visited Moorfields Eye Hospital and learned the technique. As a result, the therapeutic abilities offered by BoNT-A were rapidly disseminated worldwide.

The Development of AbobotulinumtoxinA

The UK doctors who trained with Scott soon realized the significant potential offered by BoNT-A as a therapeutic option for several difficult-to-treat diseases. This led to collaboration between these pioneering clinicians and the Centre for Applied Microbiology and Research (CAMR) at Porton Down, United Kingdom. CAMR provided BoNT-A for the Moorfields study, for example. 12

The production process used by CAMR was different from that devised by Schantz to supply Scott, and was based on work on vaccines against BoNT in the 1980s. 40 In 1984, a biotechnology company called Porton International (whose successor was eventually purchased by Ipsen SA in France) formed a partnership with CAMR. 12 Among other products, Porton International developed and commercialized ABO as Dysport (Dystonia/Porton Down; Ipsen Biopharm Ltd, Wrexham, UK). Dysport proved to be effective in a range of dystonic conditions, including blepharospasm, hemifacial spasm, cervical dystonia, Meige syndrome, oromandibular dystonia, and writer’s cramp. 41-43 Based on this compelling evidence, Dysport was approved in Europe for the treatment of specific dystonias in December 1990. Dysport now has marketing authorizations in 75 countries. In 2007, Ipsen (now the manufacturers of Dysport) entered a partnership with Galderma to develop, promote, and distribute ABO for aesthetic indications, a relationship that continues today and has expanded into many markets around the world.

BoNT in Aesthetic Medicine

The potential offered by BoNT in aesthetic medicine first emerged soon after Scott’s pioneering work with strabismus. A detailed discussion of the evidence base supporting BoNT in aesthetic indications is outside the scope of this review. However, over the years, numerous multicenter, double-blind, randomized, placebo-controlled studies have confirmed that BoNT injections are safe and effective in reducing the severity of glabellar lines and in other aesthetic indications. 44-48

Once again, Scott, who reportedly used BoNT for aesthetic reasons in the mid-1980s, led the way. 49 Anecdotally, an author of this paper, A. Pickett, heard from colleagues that several patients being treated for blepharospasm and hemifacial spasm reported that their wrinkles and migraines had improved after receiving BoNT. Similar reports led several clinicians (including Theodore Tromovitch and the Carruthers) to consider the aesthetic possibilities of BoNT. 49 Researchers at the Columbia-Presbyterian Medical Center in New York, for example, noted that, after treatment with BoNT, patients with blepharospasm, Meige syndrome involving the upper or lower part of the face, hemifacial spasm, and post-Bell’s palsy facial synkinesis “also displayed a loss of wrinkles or hyperfunctional lines.” 50

The first formal report of a possible aesthetic use for BoNT emerged from Richard Clark and Craig Berris at the University of California, Davis, in 1989. A 52-year-old woman had undergone a second face lift and orbicularis plication for crow’s feet. This resulted in left frontal nerve paralysis. 51 Clark and Berris injected BoNT-A into the contralateral functioning frontalis muscle, which produced a satisfactory improvement in the excessive wrinkling and exaggerated frowning of the forehead caused by contraction of the frontalis, corrugators, and depressor supercilii muscles. 51,52 Their paper, submitted to Plastic and Reconstructive Surgery in January 1988, 30 is, to the best of the authors’ knowledge, the first documented use and first peer-reviewed publication of BoNT-A for an aesthetic indication.

Numerous publications soon followed from various centers. In January 1992, Carruthers and Carruthers reported that BoNT-A injections improved glabellar frown lines in 17 patients over 3 to 11 months. 53 In April of the same year, researchers at Columbia-Presbyterian Medical Center described the use of BoNT-A in hyperfunctional lines associated with the frontalis musculature and platysma during the American Academy of Facial Plastic and Reconstructive Surgery conference in Palm Springs. All patients experienced partial or total resolution of painful contractions or unsightly hyperfunctional lines and spasms, the effect lasting for 3 to 6 months. 30 Researchers at Boston University assessed the BoNT dose-response relationship for the glabellar area in women. They reported a starting dose of 2.5 to 4 units per injection site, which produced a duration...
of effect of 2 to 5 months. The FDA approved Botox Cosmetic (onabotulinumtoxinA) for glabellar lines in 2002.

In Europe, the development and marketing of ABO initially focused on dystonia and oculor indicatons. In 2003, however, Dewandre et al reported results from a pilot study that showed that ABO was effective in forehead and glabellar lines and crow’s feet. A large German study, published in 2006, enrolled 221 patients and confirmed the efficacy of ABO in moderate or severe glabellar wrinkles. In this study, 73 patients received ABO and 37 received a placebo injected into 3 sites in the procerus and corrugator muscles. After 4 weeks, the proportions of responders were 86.1% and 18.9%, respectively. A further 73 and 38 patients received ABO and placebo, respectively, into these 3 sites as well as 2 additional sites 1 cm cranial from the corrugator sites. After 4 weeks, the proportions of responders were 86.3% and 7.9%, respectively. ABO was well tolerated and free from major adverse effects.

ABO was first launched for the aesthetic indication of treatment of glabellar lines in Germany in 2006. It was subsequently authorized across Europe in 2009 as Azzalure (Galderma, Paris, France) for the treatment of moderate-to-severe glabellar lines, when the severity of these lines has an important psychological impact on the patient. The brand Azzalure is marketed for aesthetic indications in the European Union, and elsewhere Dysport is the common tradename for aesthetic or therapeutic applications. The European regulators required 2 different product names to avoid confusion between the medical and aesthetic indication and to deter use of the high-dose vial as a multidose presentation. Interestingly, no other regulatory authorities in the world followed suit.

In 2009, the American product Botox was designated onabotulinumtoxinA and the UK version, Dysport, as ABO. Several other versions of BoNT are now available, including rimabotulinumtoxinB and incobotulinumtoxinA. The nomenclature stems—ona, abo, rima, inco etc.—reflect the need for approved United States Adopted Names to differentiate the BoNT products. The Speywood unit (s.U), a measure of the biological potency used for ABO products, is unique to the Dysport/Azzalure product family and is not interchangeable with other BoNT preparations.

FUTURE DEVELOPMENTS

Several developments relevant to the use of BoNT will probably reach the clinic over the next few years, most notably several so-called “biosimilars” from a range of manufacturers. In reality, no new BoNT product can be a biosimilar because the potency units of each product are specific to that product and are not interchangeable, a fact that is heavily stressed by regulatory authorities and included as clear statements on any prescribing information.

The oldest biosimilar BoNT-A is BTXA from the Lanzhou Institute of Biological Products in China, which was first licensed in 1997 and is otherwise known as “Hengli” toxin. BTXA uses dextran and gelatine as stabilizers instead of the traditional human serum albumin included in almost all other formulations of BoNT-A. The presence of gelatine may be unacceptable to some cultural and religious groups. In addition, gelatine confers an increased risk of allergic reactions, including anaphylactic shock. One patient has been reported to have developed urticarial plaques proximal to the injection site when this product was used, emphasizing the immunogenic potential. Most use is uneventful. Nevertheless, these allergic reactions demonstrate that BoNT products with different formulations are not readily interchangeable.

Three Korean BoNT-A biosimilars have been developed that use different manufacturing processes and strains of C. botulinum. Even minor changes between the reference product and the biosimilar can potentially affect the pharmacokinetics, pharmacodynamics, clinical efficacy, and tolerability, including immunogenicity. The postmarketing monitoring, risk management, and risk mitigation plans for biosimilar BoNT should include immunogenicity assessments. Unfortunately, no standardized potency assay has ever been internationally adopted, which hinders comparisons of the growing number of BoNT products. In addition, some of these new products are only supported by limited scientific and clinical evidence in the regular peer-reviewed literature. For example, there are reportedly many publications about the Chinese product in China, but unfortunately these publications are not accessible to the rest of the world.

New Therapeutic Types and Applications

Research into the therapeutic applications of other BoNT types has also been reported. Ludlow et al published the first report of the therapeutic use of BoNT-F in 1992. They treated 4 patients—with torticollis, oromandibular dystonia, or stuttering—who had developed antibodies to BoNT-A. The time to full return of symptoms varied from 30 to 82 days. This relatively short duration of action meant that BoNT-F was never commercialized. RimabotulinumtoxinB has been assessed clinically for aesthetic indications, but is not widely used in aesthetic practice. In 2006, Eleopra et al reported that BoNT-C was effective in 4 patients with blepharospasm and 10 patients with cervical dystonia who exhibited resistance to BoNT-A. The profile of action appears to be similar to BoNT-A.

Innovative formulations of well-established BoNT types are also likely to reach the market over the next few years. For example, Phase III aesthetic trials are currently under way with a liquid version of Dysport (Dysport Next Generation [DNG]) in moderate-to-severe glabellar lines (ClinicalTrials.gov references NCT02353871 and NCT02493946). Galderma have also announced the clinical trials of a liquid, high-purity BoNT product. Current
commercially available BoNT formulations are powders that are reconstituted with saline before use. The development of a high-purity liquid BoNT formulation offers the potential for a ready-to-use product that may result in a better patient experience and improved outcomes. The Galderma product is currently in Phase II clinical trials to evaluate the safety and effectiveness for the treatment of glabellar lines. Results are not yet available.

In addition, Revance (Newark, NJ), among several other companies, have been developing topical BoNT-A, which appears to be safe and, based on initial results, effective for axillary hyperhidrosis. At 4 weeks, 10 axillae treated topically with BoNT-A showed a 65.3% mean reduction in sweating compared with a 25.3% mean reduction when the same patients received vehicle controls. However, transdermal BoNT delivery appears to be highly inefficient. The topical dose is equivalent to approximately 2500 ABO units per administration, compared with approximately 60 units of an injected product in the crow’s feet area. However, initial results from the Phase III REALISE 1 placebo-controlled study (NCT02580370), including 450 individuals with moderate-to-severe crow’s feet, did not achieve the primary or other endpoints. Revance Therapeutics, Inc. have therefore disclosed that they do not plan to continue development of RT001 topical for crow’s feet, or to pursue the current clinical development plan for RT001 in axillary hyperhidrosis.

The range of therapeutic uses for BoNT continues to expand. A detailed examination is outside the scope of this review, but 3 examples illustrate the significant potential (these are currently all experimental, unapproved indications). Two of these new potential applications relate to improvements in skin quality.

For example, several studies suggest that BoNT is an effective treatment for psoriasis. In one study, all 15 patients with a confirmed diagnosis of inverse psoriasis showed improvements in subjective symptoms, and 13 patients showed improvements in erythema extension, intensity, and infiltration. Treatment was well tolerated.

Secondly, a growing body of evidence suggests that BoNT reduces sebum production. Min et al, for example, reported that BoNT-A significantly reduced sebum production at the injection site but increased the sebum production of the surrounding skin. Clinical studies are now under way to assess BoNT-A in psoriasis (NCT00816517) and acne (NCT00765375).

More recently, a UK team reported that injecting ABO into the tensor fasciae latae, followed by physical therapy, significantly improved symptoms of patellofemoral overload syndrome that failed to respond to conventional treatment. The effect lasted for up to 5 years. These types of new uses can be considered pioneering applications of such a high-potency biological product in debilitating conditions.

**CONCLUSIONS**

As these examples illustrate, more than 40 years after Scott’s pioneering animal experiments, 27 years after the first formal report of a possible aesthetic use for BoNT-A, and 25 years after the introduction of ABO, the therapeutic use of BoNT continues to develop in aesthetic medicine and beyond. The final chapter in the history of BoNT is some way from being written.

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