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The 200-Year Timeline on Botulinum Toxin: From Biologic Poison to Wonder Drug

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ABSTRACT

The history of botulinum toxin dates back to the late 1700s, when food preparation, storage, and later canning practices led to outbreaks of botulism across Europe and the United States. It is from these initial incidents that the remarkable discovery of botulinum toxin was eventually made, sparking over 200 years of further scientific inquiry and medical innovation. To date, 6 botulinum toxin products have been commercialized in North America with numerous indications across the specialties of ophthalmology, neurology, urology, dermatology, plastic surgery, and otolaryngology. This article traces the key moments and important players in the remarkable journey of this biologic poison and wonder drug.

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INTRODUCTION

The global medical botulinum toxin market is currently valued at 5.8 billion USD and is expected to rise to 15 billion USD by the year 2030.[1] From its beginnings as a deadly food-borne toxin, botulinum toxin (BoNT) has had a revolutionary journey to its current powerful and versatile iteration, with indications for numerous cosmetic and medical applications.[2-4] As future strides are made in novel uses and approvals for BoNT,[5-7] it is worth remembering the historical foundation on which we stand, from the isolation of the toxin to the remarkable experiments that ultimately led to its pervasive medical use, summarized in Table 1.

Commentary

The history of BoNT can be viewed as four distinct transformational stages:

1) Outbreaks of food poisoning led to the seminal discovery and isolation of the toxin (1793 – 1920s)

From the late 1700s to the early 1900s, multiple food-associated epidemics occurred across Europe and the United States of yet unknown cause, with numerous fatalities. Through experiments on animals and himself, Dr Justinius Kerner of Germany was the first to surmise the ultimate source of a sausage-poisoning epidemic was a biologic toxin acting on nerve signals to cause multi-organ and respiratory failure.[8] Later on, Emile Pierre-Marie van Ermengem in Belgium identified Clostridium botulinum as the bacteria producing the exotoxin, and Dr Hermann Sommer of the US isolated the first crude form of botulinum toxin type A (BoNT-A).[9]

2) Threat of BoNT use in biological warfare (1940s–1970s)

After the bombing of Pearl Harbor by the Japanese in World War II, the US government placed increased attention on the covert study of wartime threats for offensive and defensive reasons, including the study of lethal toxins and biological agents, due to fears that the Germans were weaponizing such toxins and agents against Americans. A team of scientists including Carl Lamanna, Arthur Guyton, and Edward Schantz worked jointly at the U.S Biological Warfare Center to culture the first purified stores of BoNT-A and further study its physiologic effects in humans. When fears of the Germans using weaponized botulinum toxin were proven to be unfounded, the Americans abandoned the study of the use of the toxin for warfare.[10-11] At the end of World War II in 1945 when the covert toxin experimentation concluded at Camp Detrick, Dr Schantz became the custodian for the remaining stores of purified BoNT-A. Starting in the 1950s and throughout his career after leaving Camp Detrick in 1972, he shared the toxin with qualified physicians and scientists for research purposes, sparking the next stage in the history of botulinum toxin.[9] Dr Arnold Burgen in the UK, Dr Vernon Brooks in Canada, and Dr Daniel Drachman in the US performed separate experiments to collectively elucidate the effect of BoNT on neuronal synaptic terminals and its ultimate denervation of muscles through the neuromuscular junction.[12-15]

3) Animal and human clinical trials spearheaded by ophthalmologist Dr Alan Scott (1972 – 1989)

Dr Alan Scott, an ophthalmologist and researcher at the Smith-Kettlewell Eye Research Institute in San Francisco who had been working since the 1960s to find a novel surgery-sparing therapeutic to treat strabismus, learned of the effect of botulinum toxin on muscles and requested samples of BoNT-A from Dr Schantz.[9] After successful results in Rhesus monkeys, Dr Scott published his breakthrough primate research in 1973.[16] This research ultimately led to Food and Drug Administration (FDA) approval of the first human clinical trial of BoNT. In 1978, Dr Scott became the first to inject medicinal botulinum toxin

TABLE 1.

Key Moments in the History of Botulinum Toxin From 1793 – 2021	
Factor	**Score**
1793	Outbreak in Wildbad, Germany. Six people die from botulism poisoning associated with blood sausage.
1822	Justinius Kerner, a physician in Germany, performs animal experiments and deduces that botulinum toxin acts by interrupting nerve signal transmission.
1895	Three musicians die from botulism in Ellezelles, Belgium after eating raw ham.
1895-1897	Professor Emile Pierre-Marie Van Ermengem from University of Ghent identifies Clostridium botulinum in ham.
1919-1920	Food poisoning deaths from California-produced black olives occurring in Ohio, Montana, Michigan, Tennessee, and New York.
1926	Dr Hermann Sommer isolates a crude form of botulinum toxin.
1943	US chemical warfare research facility established at Camp Detrick in Frederick, Maryland.
1943-1946	Carl Lamanna purifies botulinum toxin A at Camp Detrick.
1943-1946	Arthur Guyton develops evidence of how botulinum toxin affects acetylcholine at the neuromuscular junction.
1947	Dr Schantz prepares and maintains a pure culture of botulinum A toxin.
1950	Dr Schantz begins sharing toxins for research and food safety purposes. This continues until 1994 when the supply was exhausted. Dr Schantz would provide botulinum toxin A to 150 researchers worldwide.
1950s-1960s	Drs Arnold Burgen, Vernon Brooks, Dan Drachman separately carry out experiments to describe the effect of botulism on muscle.
1961	Dr Alan Scott, a young ophthalmologist at the Smith-Kettlewell Eye Research Institute in San Francisco, California, begins studying the extraocular muscle in humans and animal models.
1971	Dr Schantz retires as Chief of Fort Detrick Lab. He takes botulinum A culture with him to his new post at the Food Research Institute at the University of Wisconsin-Madison and continues as the custodian of the toxin.
1972	Dr Scott contacts Dr Drachman and upon his advice, receives botulinum toxin A culture from Dr Schantz and injects the extraocular muscle of Rhesus monkeys.
1973	Dr Alan Scott reports on his use of botulinum toxin at annual meeting of the Association for Research in Vision and Ophthalmology and publishes his groundbreaking work.
1977	New drug approval (IND) status for botulinum toxin A granted to Dr Scott.
1978	FDA clinical trials begin in humans. Dr Scott injects the lateral rectus muscle of a 26-year-old man with strabismus after retinal detachment surgery. He is the first person to receive medicinal botulinum toxin A.
1981	Dr Scott's seminal paper on the results of his human clinical trial of botulinum toxin is published after treating 147 patients.[18]
1981-1983	Dr Scott names botulinum toxin A, "Oculinum", and forms a corporation of the same name to keep up with testing and manufacturing operations and facilitate FDA approval to meet demand of clinical trial.
1982	Dr Scott expands clinical research team with voluntary contributions from researchers to grow the clinical trial.
1982	Dr Jean Carruthers, a Canadian ophthalmologist, spends several months studying with Dr. Alan Scott in San Francisco. She observes Dr. Scott's clinical trial patients who were treated for strabismus, dystonia, and muscle spasms. Dr Scott invites Dr Carruthers to join this clinical trial.
1989	First FDA drug approval for botulinum toxin A for treatment of blepharospasm and strabismus in patients 12 years and older, following the results of Dr Scott's pivotal trial.
1989	Allergan forms distribution agreement with Oculinum, Inc.
1991	Oculinum is acquired by Allergan for $9M. Dr. Scott estimated total cost of the drug development from 1971 to 1990 to be $4M. Allergan changes name of Oculinum to Botox.
1991	Dr Carruthers presents on cosmetic use of botulinum toxin at Annual Meeting of American Society for Dermatologic Surgery.
1994	Allergan develops new botulinum culture as Dr Schantz's original toxin culture runs out. Allergan production plant is in Westport, Ireland.
2000	Botox and Myobloc are approved for treatment of cervical dystonia
2001	Botox is approved for cosmetic use in Canada.
2002	Botox becomes first botulinum toxin approved for cosmetic use in USA. First cosmetic approval is for glabellar lines.
2004	Botox is approved for treatment of primary axillary hyperhidrosis.
2009	Dysport is approved for treatment of cervical dystonia. Dysport receives first cosmetic approval for treatment of glabellar lines.
2010	Botox is approved for treatment of chronic migraine and upper limb spasticity in adults. Xeomin is approved for treatment of cervical dystonia and blepharospasm.
2011	Botox is approved for treatment of urinary incontinence due to neurologic conditions. Xeomin receives first cosmetic approval for treatment of glabellar lines.
2013	Botox is approved for treatment of overactive bladder. Botox receives second cosmetic approval for treatment of lateral canthal lines.
2015	Dysport and Xeomin is approved for treatment of upper limb spasticity in adults.
2016	Botox is approved for treatment of lower limb spasticity in adults. Dysport is approved for treatment of lower limb spasticity in pediatrics.
2017	Dysport is approved for treatment of lower limb spasticity in adults. Botox is approved for cosmetic treatment of forehead lines.
2018	Xeomin is approved for treatment of chronic sialorrhea in adults.
2019	Botox is approved for treatment of upper and lower limb spasticity in pediatrics. Myobloc is approved for treatment of chronic sialorrhea.
2019	Jeuveau receives first cosmetic approval for treatment of glabellar lines.
2019	Abbott Laboratories purchases Allergan for $63 billion, and spins off subsidiary Abbvie as pharmaceutical arm, overseeing Botox. Abbvie retains the brand name of Allergan for marketing purposes.
2020	Xeomin is approved for treatment of chronic sialorrhea in pediatrics.
2021	Botox is approved for treatment of destrusor overactivity associated with a neurologic condition in pediatrics.
2021	Dr Alan Scott dies.

FIGURE 1. Timeline of FDA approvals of medical indications for botulinum toxin, 1989 – 2021.

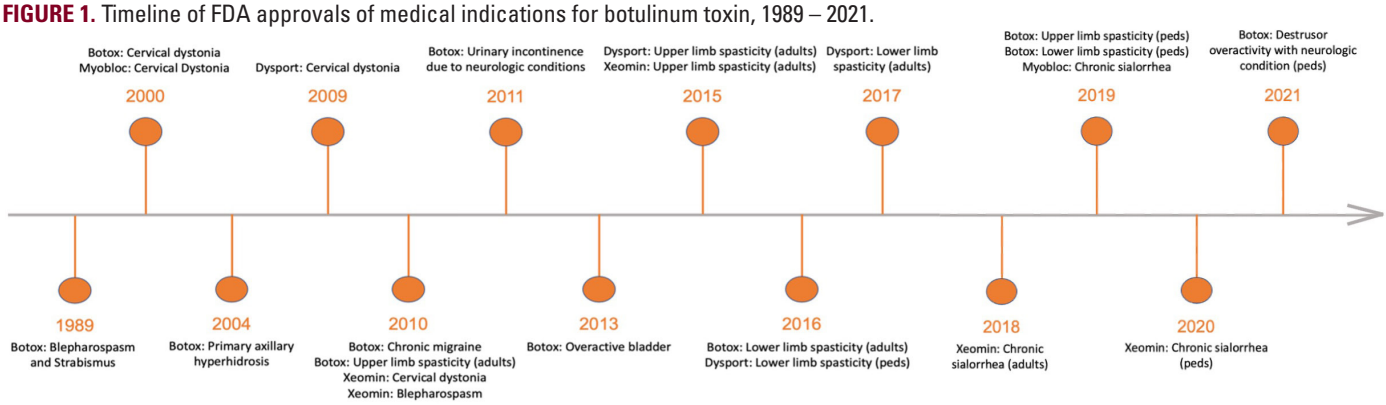
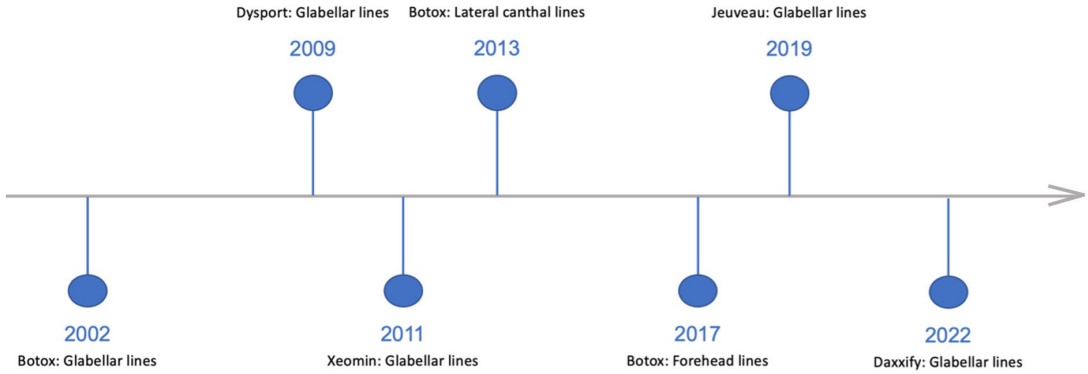


FIGURE 2. Timeline of FDA approvals of cosmetic indications for botulinum toxin, 2002 – 2022.



into human subjects, with safe and effective results. In 1981, he published his seminal clinical trial results.[17] After this initial success, more physicians joined Dr Scott's strabismus clinical trials as clinical investigators, including Dr Jean Carruthers, a Canadian ophthalmologist, who would go on to collaborate with her dermatologist husband, Dr Alistair Carruthers, in studying and popularizing the use of BoNT in cosmetic dermatology. Though aware of the aesthetic potential of BoNT for facial muscles and rhytides, Dr Scott expressed no interest in pursuing this indication himself.

4) BoNT as a wonder drug: FDA approvals (1989 – Present)

In 1989, the FDA issued the first landmark approval of BoNT-A for blepharospasm and strabismus associated with dystonia in patients twelve years and older. Numerous other medical and cosmetic indications followed in the coming decades. By the time of Dr Alan Scott's passing in 2021, 5 different commercial products of BoNT (Botox® (onabotulinumtoxin-A, Abbvie/Allergan Aesthetics), Dysport® (abobotulinumtoxin-A, Galderma), Xeomin® (abobotulinumtoxin-A, Merz Pharmaceuticals), Jeuveau® (prabotulinumtoxin-A, Evolus), and Myobloc® (rimabotulinumtoxin-B, Solstice Neurosciences)) would be FDA approved in the US with a combined 28 different indications across the specialties of ophthalmology, neurology, urology, dermatology, and otolaryngology (Figure 1 and 2). Most recently at the time of this writing, a 6th product, Daxxify® (daxibotulinumtoxinA-lanm, Revance), has been approved by the FDA for cosmetic indication.

DISCLOSURE

The authors have no conflicts of interest to declare.

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