

A short overview of the evolution of botulinum toxin type A formulations

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Botulinum toxin type A (BoNT-A) is a potent neurotoxin produced by the bacterium *Clostridium botulinum* [1]. BoNT-A has been used for various therapeutic and aesthetic purposes, including the treatment of muscle disorders, chronic pain and facial wrinkles [2-4]. Over the years, multiple BoNT-A products have been developed and marketed with varying degrees of safety and efficacy. All these products have differing manufacturing processes and are hence not interchangeable.

This article aims to briefly review the development and evolution of BoNT-A products, comparing their safety and efficacy in various therapeutic and aesthetic applications. The discussion spans from the early days of BoNT-A to the recent advances and emerging products in the market. Emphasis is placed on the differences in potency, formulation, and clinical applications of these products.

History of botulinum toxin type A

The history of BoNT-A dates back to the early 19th century. It has since evolved from a deadly toxin to a versatile therapeutic agent used in various medical and cosmetic applications.

Discovery (1817-1895): The story of botulinum toxin begins in 1817 when German Physician Justinus Kerner first described the clinical features of foodborne botulism, a severe paralytic illness caused by ingestion of the toxin produced by the bacterium *Clostridium botulinum* [5]. In 1895, Belgian Microbiologist Emile van Ermengem isolated and identified the causative organism, *Clostridium botulinum*, from a contaminated ham that caused a botulism outbreak [6].

Purification and classification (1920s-1940s): The first purified preparation of botulinum toxin was achieved in the 1920s by Hermann Sommer and colleagues at the University of California, San Francisco [7]. Further research in the 1940s led to the classification of botulinum toxin into seven distinct serotypes (A-G) based on their antigenic properties [7,8].

Therapeutic potential (1950s-1970s): In the 1950s, researchers began to explore the therapeutic potential of botulinum toxin. Vernon Brooks discovered that BoNT-A could selectively block the release of acetylcholine at neuromuscular junctions, causing temporary muscle paralysis [9]. This discovery laid the foundation for the development of BoNT-A as a therapeutic agent.

Clinical use (1980s-present): In 1989, the US Food and Drug Administration (FDA) approved onabotulinumtoxinA (Botox®) for the treatment of strabismus and blepharospasm [10]. Since then, the clinical use of BoNT-A has expanded to include various medical and cosmetic applications, such as the treatment of cervical dystonia, chronic migraine, overactive bladder, and facial wrinkles [3,11].

New formulations and future developments: In recent years several BoNT-A formulations have been developed, each with unique properties and characteristics. Ongoing research aims to improve the safety and efficacy of these products and explore new therapeutic applications [12,13]. With the ongoing research and introduction of new formulations, the therapeutic potential of BoNT-A continues to expand, providing effective treatment options for a wide range of medical and cosmetic applications. As understanding of this versatile neurotoxin grows, it is likely that we



will continue to witness new applications and improvements in the safety and efficacy of BoNT-A products.

The various BoNT-A formulations

OnabotulinumtoxinA (Botox® / Vistabel®): This is a vacuum-dried powder formulation of BoNT-A produced by Allergan Inc. (Dublin, Ireland). Botox has been widely used for therapeutic and aesthetic purposes for many years, with its safety and efficacy well-established [2,14].

AbobotulinumtoxinA (Dysport® / Azzalure®): This is a lyophilised powder formulation of BoNT-A developed by Ipsen (Paris, France) and Galderma (Lausanne, Switzerland). Dysport has demonstrated safety and efficacy comparable to OnabotulinumtoxinA in various studies, although it exhibits different diffusion / spread properties, potentially leading to different clinical outcomes [15,16].

AbobotulinumtoxinA injectable solution (Alluzience®): This is a liquid form of botulinum toxin type A (Galderma, Lausanne, Switzerland). Owing to its liquid state, it offers the possibility of enhanced safety and dosing precision in comparison to freeze-dried BoNT-A formulations.

IncobotulinumtoxinA (Xeomin® / Bocouture® / NT 201): This lyophilised powder formulation of BoNT-A is produced by Merz Pharmaceuticals GmbH (Frankfurt, Germany). Xeomin contains a purified neurotoxin without accessory proteins, potentially reducing antigenicity and adverse reactions [17]. Seo et al. compared the safety and efficacy of Xeomin with Botox and Dysport, finding it to be effective, but with differences in potency, immunogenicity, and diffusion / spread [18].

PrabotulinumtoxinA (Nuceiva® / Jeuveau®): Developed by Daewoong Pharmaceutical Co., Ltd. (Seoul, South Korea), this lyophilised powder formulation of BoNT-A aims to improve upon the safety and efficacy profiles of its predecessors. In 2018 Dhillon

et al. discussed the potential advantages of PrabotulinumtoxinA in specific clinical applications due to its field of action [13], while in 2020 another study compared reported safe, effective and non-inferior results for PrabotulinumtoxinA in comparison to OnabotulinumtoxinA for the treatment of moderate to severe glabellar lines in adults [19]. Other studies have also reported on the safety and efficacy of PrabotulinumtoxinA [20-22].

DaxibotulinumtoxinA (DAXXIFY™, RT002): This lyophilised powder formulation of BoNT-A is produced by Revance Therapeutics, Inc. (USA). It is a highly purified 150-kDa core neurotoxin derived from the Hall strain of *Clostridium botulinum*. Several studies have reported high efficacy and safety rates along with good tolerance levels for DaxibotulinumtoxinA [23-25].

LetibotulinumtoxinA (Botulax / Hutox and Letybo): Both of these lyophilised powder formulations of BoNT-A are produced by Hugel Pharma (Korea). Croma Pharma has licensed the product from Hugel Inc. (Letybo). Their safety and efficacy profiles are currently being evaluated with one study demonstrating high efficacy and a convincing safety profile in the treatment of glabellar lines [26].

Neuronox and Innotox: These lyophilised powder and liquid formulations of BoNT-A are produced by Medytox (Korea). Research on these products is ongoing, with some studies showing promising safety and efficacy results in various therapeutic and aesthetic applications [27,28].

Duration of effect of different BoNT-A formulations

The duration of effect of BoNT-A formulations varies depending on the specific product, the treated condition, the injected dose, and individual patient factors. Here, we discuss the duration of effect for some of the most commonly used BoNT-A formulations:

OnabotulinumtoxinA (Botox® / Vistabel®): The duration of effect for Botox® generally ranges between three to six months, depending on the treated condition and the injected dose. In cosmetic applications, such as the treatment of facial wrinkles, the effect typically lasts for about three to four months [29,30]. For medical conditions like cervical dystonia or chronic migraine, the duration of effect may extend up to six months [31,32].

AbobotulinumtoxinA (Dysport® / Azzalure®): Similar to Botox, the duration of effect for Dysport® typically ranges from three to six months. In cosmetic applications, the effect lasts for approximately three to four months [33]. For medical conditions the duration of effect can extend up to four to six months [11].

IncobotulinumtoxinA (Xeomin® / Bocouture® / NT 201): The duration of effect for Xeomin is comparable to that of Botox and Dysport. In cosmetic applications, the effect generally lasts for about three to four months [34]. In the treatment of medical conditions the duration of effect can last for up to six months [35].

PrabotulinumtoxinA (Nuceiva® / Jeuveau®): The duration of effect for Nuceiva appears to be similar to that of other BoNT-A formulations, with effects lasting for approximately three to four months in cosmetic applications [36].

DaxibotulinumtoxinA (DAXXIFY™, RT002): DaxibotulinumtoxinA has shown promise in providing a longer duration of effect compared to other BoNT-A products. In a phase three clinical trial for glabellar lines, the median duration of effect was found to be approximately 24 weeks so roughly six months [37].

As newer formulations of BoNT-A are being developed, their duration of effect and efficacy in various applications may differ from those of the more established products. Research is ongoing, and additional clinical studies may provide further insights into the comparative performance of these formulations.

It is essential to consider that the duration of effect for BoNT-A formulations can vary among individuals due to factors such as age, muscle mass, and metabolism. Furthermore, the injected dose, dilution, and injection technique can also influence the

duration of effect. Clinicians should tailor treatment plans based on individual patient needs and the specific indications for which BoNT-A is being used. Emerging formulations show promise in providing a longer duration of effect, which may expand the range of applications and improve patient satisfaction with treatment outcomes.

Immunogenicity and BoNT-A formulations

Immunogenicity refers to the ability of a substance to provoke an immune response in the body. Immunogenicity is an important consideration in the selection of BoNT-A formulations for clinical use.

With relation to BoNT-A injections, immunogenicity can lead to the development of neutralising antibodies against the neurotoxin, potentially reducing its therapeutic effectiveness and increasing the risk of treatment failure [38,39].

Different BoNT-A formulations exhibit varying degrees of immunogenicity due to differences in their composition, including hypotheses regarding the presence or absence of complexing proteins and other impurities [17,40]. The use of lower doses and less frequent injections might help minimise the risk of antibody formation [38].

Conclusion

BoNT-A products have evolved significantly since their initial introduction for therapeutic and aesthetic applications. While older formulations like Botox®, Dysport® and Xeomin® have demonstrated proven safety and efficacy, newer products and emerging formulations from Korea and China are aiming to improve upon these profiles. The products are all unique and are not interchangeable. Differences in potency, immunogenicity, field of effect and spread / diffusion / migration impact the clinical performance of all formulations. Continued research is essential to optimise the safety and efficacy of BoNT-A products, ensuring they meet the diverse needs of patients and clinicians.

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