SEXUAL MEDICINE REVIEWS

# Botulinum Neurotoxin and Its Potential Role in the Treatment of Erectile Dysfunction

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## ABSTRACT

**Introduction:** Botulinum toxin type A (BoNT-A) has been used to treat several striated and smooth muscle disorders. During the past year, human and animal studies conducted in Egypt and Canada by two different groups of investigators have suggested a possible role for the intracavernosal injection of BoNT-A in the treatment of erectile dysfunction (ED).

**Aim:** To discuss BoNT-A and its current medical uses, the rationale for its new potential use in the treatment of ED, and the available evidence and concerns.

**Methods:** A literature search was conducted. This review was based on the available studies presented at the European Society for Sexual Medicine, Sexual Medicine Society of North America, and International Society for Sexual Medicine meetings in 2016 by the two groups.

**Main Outcome Measures:** Sinusoidal diameter; penile color Doppler study; Erection Hardness Score; Sexual Health Inventory for Men questionnaire; and Sexual Encounter Profile questions 2 and 3.

**Results:** Two human studies conducted by the authors and two animal studies (one from the authors' group and one from Canada) were reviewed. These seemed to suggest generally favorable outcomes with the use of BoNT-A in the treatment of ED.

**Conclusion:** BoNT-A could be a potential therapy for ED. In addition to the findings of the three pilot studies, larger multicenter trials need to be conducted to further explore the true therapeutic efficacy and clinical safety of BoNT-A in the treatment of ED. **Ghanem H, Raheem AA, AbdelRahman IFS, et al. Botulinum Neurotoxin and Its Potential Role in the Treatment of Erectile Dysfunction. Sex Med Rev 2017;X:XXX–XXX.**



**Key Words:** Botulinum Neurotoxin Type A; Botox; Erectile Dysfunction; Intralesional Treatment

## INTRODUCTION

Botulinum neurotoxin (BoNT) is one of the most potent toxins known to humans. It is produced by *Clostridium botulinum,* an anaerobic spore-forming, gram-positive bacterium. Poisoning with BoNT can cause botulism, resulting in generalized paralysis including respiratory arrest and death.[1,2]

The capacity of BoNT to relax muscles has been used during the past four decades to treat several striated and smooth muscle disorders in addition to its wide use in esthetic medicine. More recently, researchers have investigated whether the muscle-relaxing capacity of BoNT could be used within the corpora cavernosa to enhance penile erections, thus introducing a possible new line of treatment for erectile dysfunction (ED). During the past year, human and animal studies have been conducted in Egypt and an animal study has been conducted in Canada by two different groups of investigators.[3–8]

## MECHANISM OF ACTION OF BONT

There are seven distinct biochemical and serologic forms of BoNT (A, B, C1, D, E, F, and G). BoNT-A, BoNT-B, and BoNT-E can cause botulism in humans, whereas the remaining BoNT forms can cause disease only in animals. BoNT-A is the most commonly used form in medicine.[9,10]

The seven BoNT forms cause flaccid paralysis by preventing the release of acetylcholine at the presynaptic membrane. They act on different aspects of the soluble N-ethylmaleimide sensitive

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factor attachment protein reception (SNARE) complex. The SNARE complexes are important groups of polypeptides that mediate the fusion of the synaptic vesicle to the presynaptic membrane at the neuromuscular junction, thus allowing acetylcholine release into the synaptic cleft. The SNARE complex influenced by BoNT-A is synaptosome-associated protein-25 (SNAP-25; Figure 1).[11,12]

BoNT-A is formed by a heavy polypeptide chain and a light polypeptide chain joined by a disulfide bond. The heavy chain has high affinity to cholinergic neurons and forms an irreversible bond at the presynaptic surface with synaptic vesicle protein-2. Once this bond is formed, the toxin-receptor complex can enter the cell through the process of endocytosis. When the complex enters the cytoplasm, the disulfide bond breaks, separating the heavy and light chains. It is the light chain that interacts and cleaves SNAP-25. Once BoNT-A has cleaved the polypeptide of SNAP-25, the presynaptic nerve terminals are affected irreversibly. It takes up to 3 months for the production of new nerve terminals, at which point function returns.[11,12] The polypeptides of SNAP-25 and synaptic protein-2 are central to the effect of BoNT-A. They have been identified in the urothelium of human bladders and are found widely throughout various smooth muscles.[13]

The inhibitory effects of BoNT on the release of acetylcholine from parasympathetic and cholinergic neurons are well understood. There also is evidence suggesting that BoNT can inhibit noradrenaline, dopamine, glycine, and γ-aminobutyrate. The effect on these additional neurotransmitters is often less profound than on acetylcholine and is dose and site specific. BoNT has been used for prostatic smooth muscle relaxation in the management of lower urinary tract symptoms.[14] It also has been found to inhibit noradrenaline release in the urethra and anococcygeus of rats[15,16] and prostatic tissue of dogs.[17] The duration of effect of BoNT-A in striated muscle is roughly 2 to 3 months; however, in smooth muscle, its effects are believed to last longer.[11]

## CURRENT MEDICAL USES OF BONT

BoNT-A is the most commonly used serotype for medical application and was the first to be licensed for medical use. There are several commercially available forms; Botox (Allergan Pharmaceuticals, Parsippany, NJ, USA) is the most widely used and has the most medical applications. Different formulations of BoNT-A are available, each produced by a different company. Each formulation varies slightly in structure, efficacy, duration, and safety profile.[13] The effect of BoNT is site specific; it is administered by local injection (subcutaneous or intramuscular) into the targeted area. It can be administered using endoscopic procedure and by injection directly through the skin. Given the high affinity of BoNT to cholinergic neurons, its effects are consistent and, given at a low dose, have limited systemic adverse effects.[9]

BoNT-A was first used in medicine in 1977 for the treatment of strabismus in children. Since then, it has been widely used for different conditions and by different specialties. It is best known for its use in the cosmetic industries; however, it also is established practice in the treatment of overactive striated muscles disorders, such as strabismus, esotropia, exotropia, focal dystonias, spasticity, and movement disorders.[18]

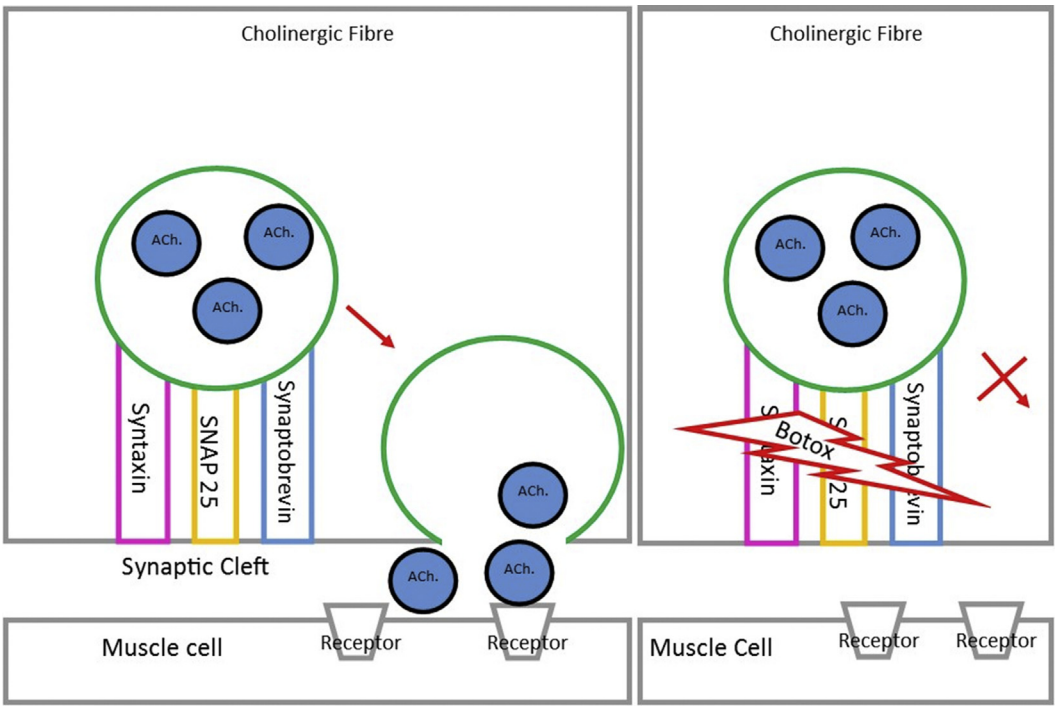


**Figure 1.** Mechanism of action of botulinum neurotoxin type A on muscle. SNAP-25 = synaptosome-associated protein-25.