

Review Article

The clinical approach to botulinum toxin in dermatology: A literature review

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ABSTRACT

Botulinum toxin (Botox) is a neurotoxin drug that is used in a wide range of cosmetic and treatment applications. This literature review provides an overview of the toxin mechanism and its effects. The popularity of toxin usage has been tremendously increasing since it is a minimally invasive procedure. Application of the toxin is primarily utilized for cosmetic purposes, to treat disorders, and as a surgery alternative. The toxin myths such as frozen face have been elaborated, as it is critical to understand the outcomes of the procedure. The toxin is generally considered to be safe, but complications can occur as well, ranging from reactions due to injections to the undesired effects produced by this toxin. Preventive strategies, such as appropriate toxin application techniques, must be considered for safety and prevention. The contraindications to the use of the toxin are also noted in the study.

Keywords: Botulinum toxin, Dermatology, Therapies, Popularity, Indications

INTRODUCTION

Botulinum toxin (Botox) is a neurotoxin drug derived from the bacterium *Clostridium botulinum* and is used for various purposes worldwide. The toxin has seven types of neurotoxins A, B, C1, C2, D, E, and G; but only two among these are used in clinical settings which are type A and B. Botox is well-known in the cosmetics industry for its usage in wrinkle reduction, filler injections, and esthetic treatments, but this review article has also focused on some of its less well-known therapeutic applications. Initially, it was introduced for treatment purposes but gained more acknowledgment in the cosmetic business for the correction of glabellar frown lines seen in 2002 by the United States Food and Drug Administration (FDA).^[1]

The toxin therapy is typically regarded as safe, efficient, and largely free of major side effects as it is a non-surgical procedure that mainly depends on the number of injections administered. However, the wide range of therapeutic and cosmetic uses of the toxins can be misused and lead to hazardous poisonous substances. Large doses of the toxin can result in botulism, a condition that paralyzes a person by disrupting the neurons that the brain uses to stimulate their muscles. The toxin injections usually cause brow ptosis and asymmetry as complications, while local injection-adverse effects can also be erythema and ecchymosis.^[2,3]

This article aims to provide a thorough assessment of the literature on the overall mechanism of action of the toxin, its statistical advantage over other treatment options, common misconceptions, side effects as well as severe complications, and various preventive actions that can be taken to deal

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with them. An additional aim is to give the readers an idea of the different varieties of the toxin available, their dilution, and the dosage of the toxin with respect to the different uses. In this literature review, we shall concentrate on both patients' and physicians' perspectives to further understand how beneficial it is and why it is recommended widely.

MATERIAL AND METHODS

Forty-four articles have been analyzed for the literature review. Keywords such as Botox, dermatology, therapies, popularity and indications were used for the literature searches in databases such as Google Scholar and PubMed.

RESULTS

According to the literature search carried out, there are enough evidence and studies suggesting that the toxin is a widespread and useful treatment in many aspects. The misconceptions relating to the toxin need to be avoided by health-care professionals and patients. The side effects and preventive measures of the toxin are well-reasoned out in this study. The complications depend on the technique used, and hence, it is important to have adequate knowledge and training on the application technique.

DISCUSSION

Mechanism of action

The mechanism of action of the toxin has been well-understood. The toxin blocks the release of acetylcholine, causing local muscle paralysis. The toxin diffuses through tissues until it selectively and reversibly binds to the pre-synaptic end of the neuromuscular junction followed by attachment to specific protein membranes involved in acetylcholine secretion. The toxin immediately inhibits the release of acetylcholine at the neuromuscular junction, resulting in reversible local relaxation of the muscles and a reduction in facial wrinkles/lines. This usually occurs from 24 h after the toxin injection has been injected, to about 2 weeks after the procedure. This effect of the toxin injection can be seen for about 3–6 months. The toxin is relatively safe and has no severe side effects. However, under certain circumstances, the effects of the toxin may wear off over time, resulting in less muscle paralysis.^[1]

The mechanism of action of the toxin includes the following four major steps:

- The first step is binding the toxin to specific receptors on the surface of pre-synaptic cells mediated by the C-terminus of the heavy chain. This step takes about 30 min.^[1,4]
- The second step is internalization, an energy-dependent receptor-mediated endocytic process. In this step, the

neuronal plasma membrane invaginates around the toxin-receptor complex, forming toxin-laden vesicles at the nerve terminal.^[1,4]

- The third step is translocation. After internalization, the disulfide bond is cleaved and the 50 kDa light chain of the toxin crosses over to the endosomal membrane of endocytic vesicles and is released into the nerve terminal cytoplasm.^[1,4]
- The final step is blocking. Serotype A and E light chains inhibit acetylcholine release by cleaving a cytoplasmic protein (SNAP-25) necessary for the docking of acetylcholine vesicles inside the neural membrane of nerve terminals.^[1,4]

Dilution, variety, and dosage

The toxin is supplied in a powdered form, which makes it important to be diluted before administration. The toxin is generally supplied in a 50-unit vial or a 100-unit vial. One vial that consists of 100 units of neurotoxin complex produced by the bacteria is purified. 0.5 mg of albumin (human) and 0.9 mg of sodium chloride is added. No preservatives are added; hence, the vial is stored in a sterile, vacuum-dried form. The lethal dose according to a study is considered to be 2500–3000 units of the toxin for an individual of weight 70 kg.^[5]

According to the United States FDA, there are three formulations of the toxin approved for therapeutic purposes. Onabotulinum toxin A (ONA; Botox[®]/Vistabel[®]), Abobotulinum toxin A (ABO; Dysport[®]/Azzalure[®]), and Incobotulinum toxin A (INCO; Xeomin[®]/Bocouture[®]) are the three types available produced by type A toxin. ONA and ABO are required to be stored at special temperatures, whereas INCO can be stored at room temperature.^[6] The formulation produced by type B toxin is neurobloc, which is indicated for the treatment of cervical dystonias in adults. The indications for this toxin remain limited and the toxin should be stored at 2–5°C. ONA is the most commonly used variety in India.^[7]

The standard dose for toxin usage is 20 units,^[1] the minimum dose for treating glabellar frown lines is 20 units. It was found that dosing 20–40 units of the toxin was more effective than 10 units alone for reducing glabellar frown lines.^[8] Botox A dosage is effective when started from 40 units for male patients. Men require higher doses of the toxin as they have a greater muscle mass than women.^[4,9] 1–2 sites of injection and 3–4 units of the toxin are recommended for the smaller or deeper muscles (e.g., orbicularis ori) that can be detected through electro-stimulation. For larger muscles (e.g. gastrocnemius), the recommended dose is 300–400 units and 4–5 injections are required to lead to a good prognosis.^[5]

Importance of surface anatomy to injectors

Botox can be used to act on a specific area of choice. Physicians need to understand the anatomical landmarks for injecting the toxin, as any carelessness could lead to muscle paralysis. The most common areas for treatment [Figure 1] are as follows:

- Forehead: The superior and frontal part of the face is the location where most treatments are performed to reduce the appearance of the facial horizontal lines
- Eyebrows: Glabella, or “11” lines, this site is generally injected to reduce the wrinkles related to looks of anger and agitation
- Crow’s feet: On the corners of the eyes, the orbicularis oculi muscle is present which is most commonly related to crow’s feet, they usually occur when one smiles
- Nasal lines: When one smiles or laughs, the nasal lines are seen on either side of the nose and are directed upward toward the eyes
- Smile lines: Lines that cause the corners of the mouth to droop, injections can be used for muscles present here, primarily the depressor anguli oris
- Lips: The use of Botox in this area can cause the lips to have an upward and outward appearance for an esthetic look.^[10]



Figure 1: Anatomical landmarks for injecting botulinum toxin. Data obtained from - Kelly W. (2020, August 20). Common Botox Injection Sites: What facial areas can be treated with Botox. <https://www.westlakedermatology.com/blog/what-areas-can-be-treated-with-botox/>.

Indications

The toxin consists of seven neurotoxins, although only toxins A and B are used clinically. Botox A is used for various ailments for cosmetic purposes in the medical field, especially in dermatology.^[1] The toxin can be used to reduce the appearance of wrinkles on the upper face,^[1,11] lichen simplex, and pompholyx (dyshidrotic eczema), raise the eyebrows, and treat problems such as hyperhidrosis and acne vulgaris.^[1,12,13] [Figure 2].

The popularity of this neuromodulator has outgrown its wide spectrum of cosmetic applications. The toxin is used to smooth out frown lines, crow's feet next to the eyes, nasolabial folds, and wrinkles on the neck and chest, including the breast.^[1,14,15] Numerous clinical indications in facial plastic surgery have been successfully effective with this neuromodulator. The toxin aids in the appearance of a “gummy smile,” to provide an esthetic appearance of the smile which is due to the overactivation of the muscles that elevate the central lip. This neuromodulator can treat facial nerve paralysis in a less invasive manner by blocking presynaptic neurotransmitter acetylcholine release, which tends to result in temporary denervation.^[16]

In addition, it can be used to decrease the appearance of wrinkles around the depressor anguli oris, nasolabial folds, dimpled chin, horizontal neck lines, platysmal bands, medial, and outer brow lift to reduce shadows on the face and smooth the jaw and cheek contours in all directions. Various studies have shown that this toxin is effective at preventing scars.^[1,17] Correction of drooping cheeks or cheek plumping can be accomplished through various methods that involve injecting Botox into the facial muscle.^[18] Botox can be considered palliative if surgical treatment is required, adjuvant if additional treatments such as orthodontic devices or lip augmentation are required, or remedial if the cause of excessive gingival display is muscular.^[19] However, it cannot be used to prevent other signs of aging such as vascular abnormalities, dry skin, and pigmentation of the skin.^[1,7]

The toxin is also used to treat conditions such as neck spasms (cervical dystonia) and lazy eyes.^[14] The toxin injections can also help prevent chronic migraines.^[14,20] Unintentional urine loss takes place, while the bladder contracts and relaxation of the muscle groups of the bladder using the toxin reduces the condition of an overactive bladder. Hyperhidrosis is a clinical disorder that comes along with immoderate sweating even without standard triggers like exercise, heat, or stress. The toxin injected into the underarm can decrease sweating. Treatment regions also can encompass the lower back and groin.^[10]

Several autonomic disorders cause glandular hypersecretion, such as gustatory sweating.^[21] It can also be used for parotid

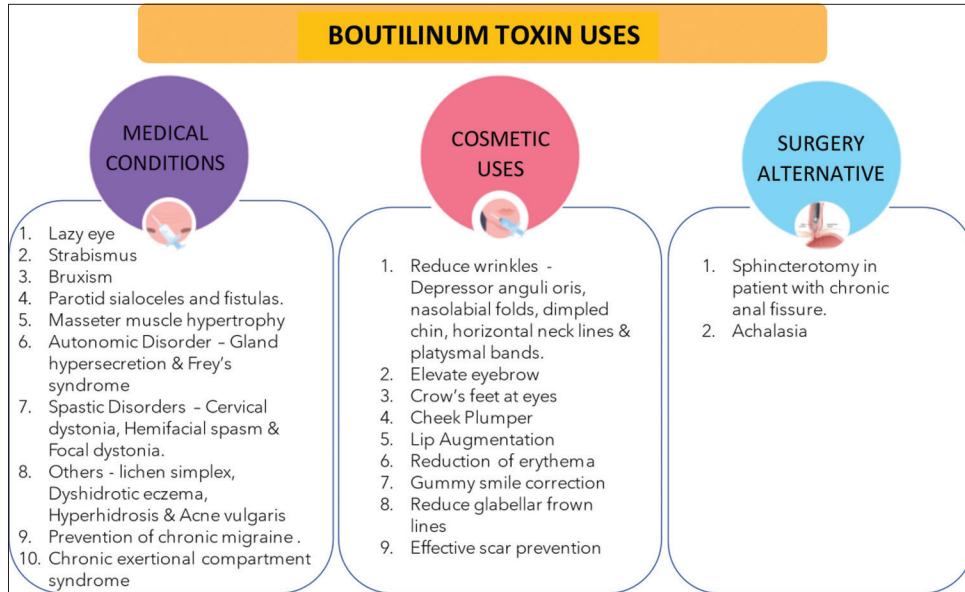


Figure 2: Indications of Botulinum toxin in the medical field.

sialoceles and fistulas.^[22] The toxin also plays a key role in treating various other diseases, especially strabismus, focal dystonia, hemifacial spasm, and various spastic movement disorders.^[14,23,24] The use of Botox-A can also reduce the frequency of bruxism episodes, indicating an improvement in patient's quality of life.^[25] Even though the complex mechanism is not fully understood, the innovative applications for Botox use in rosacea and facial flushing treatment indicate that intradermal Botox injections are safe and effective for minimizing erythema and flushing in rosacea.^[26] Intracompartmental injections of Botox type A are a good potential non-surgical therapeutic option for chronic exertional compartment syndrome.^[27] There is evident research for several other uses such as headache, hypersalivation, and some chronic conditions that are known to respond only partially to treatment.^[23]

Furthermore, it can also be used as an alternative approach to surgical intervention and appears to be a promising alternative to sphincterotomy in patients suffering from anal fissures.^[28] It is also effective for achalasia and masseter muscle hypertrophy.^[29]

The toxin is an increasingly popular procedure; recent data collection suggests that it is now the number one minimally-invasive cosmetic procedure worldwide, with almost 6 million people going through it annually.^[30] It constitutes almost 43.2% of total nonsurgical procedures in 2020.^[30]

Popularity

The popularity of toxin treatment is increasing in the current era. They are remarkably quick and easy and rarely painful. It is a prime choice for millions of women and me who want

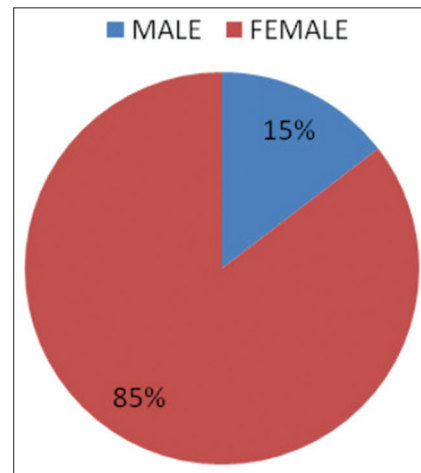


Figure 3: Comparison of Botulinum toxin Usage among men and women in 2020.^[45]

to eliminate fine lines and wrinkles without having to go through a face-lift or other cosmetic surgery.^[31] More than 5 million women and 1 million men have chosen toxin therapy as a cosmetic treatment in 2020.^[30] [Figure 3].

Until recently, the toxin usage was primarily limited to correcting muscles of facial expression over the upper one-third of the face. Since 2010, toxin injection for cosmetic usage has also started taking the role of preventative measure for signs of aging. More people in their 20s and 30s have started the usage of these injections called “Baby Botox” to supposedly curb large wrinkles from forming in the first place. While typical Botox involves injecting large amounts of it (usually onabotulinum toxin A) around the eyes and forehead to paralyze the muscles and soften or reduce the

appearance of wrinkles, “baby Botox” uses a much smaller amount. Although many studies say that the toxin can generally improve the occurrence of wrinkles on the face in the late 30s, there are very few studies that have looked at the long-term effects of preventive use in their 20s.^[32]

Misconceptions

Many people are misinformed about the toxin injections. One of these myths is that it causes a frozen face or interferes with facial expressions. The toxin only relaxes the muscles near the injection site, reducing contractions, and smoothing out wrinkles.^[33] The claim that the toxin has an immediate effect is also false, as the toxin treatments typically take 14 days to fully take effect, depending on the type of treatment. It is also claimed that the toxin treatments are only available to women. However, these treatments are becoming increasingly popular among men. The dosage used in men is reported to be relatively higher.^[34] The toxin can also be used as a preventive measure at a young age to prevent wrinkle formation later in life.

There is also a widespread misconception that the toxin is similar to botulism. Although both are produced by the same toxin, Botox is made from a purified protein derived from the toxin, and research has proven its safety and efficacy in cosmetic treatments.^[33]

Complications

Botox have been applied for upper face rejuvenation for several years. Despite their rarity, issues in this area can arise with toxin usage. A bruise in the lateral canthal region was the most frequent adverse event in this study. Other side effects of the toxin include brow ptosis, diplopia, ectropion, lagophthalmos, and xerophthalmia.^[35] [Figure 4].

A common issue that can occur when treating the frontalis muscle with the toxin is brow ptosis. Ptosis of the brow is caused by frontalis weakness.^[36] Wrong placement of injection, high dose, and improper patient selection are some of the reasons for brow ptosis.^[37]

In addition, a toxin injection into the lateral periocular area may have adverse effects such as brow ptosis, ectropion, xerophthalmia, diplopia, and lagophthalmos.^[38,39] Ectropion is caused by an unintentional weakening of the lateral orbicularis muscle sling, which can lead to secondary problems such as secondary dry eye due to extended corneal exposure. Ectropion may also happen as a result of localizing toxin diffusion following injection into the lower eyelids.^[1]

If a toxin is injected deeply into the upper lateral periocular area, where it may alter the secretions of the lacrimal gland, xerophthalmia may result. The lack of the orbicularis oculi

sphincteric function results in insufficient eyelid closure and can also cause lagophthalmos.^[3]

Asymmetry is a typical adverse reaction brought on by the location of the injection or the patient’s anatomical peculiarities. The “Spock” eyebrow, a common complication, manifests as an upward curving of the lateral brow as a result of an imbalance brought on by the lack of movement of the central frontalis and the unopposed action of the lateral frontalis, which elevates the brow tail.^[3]

The adverse effects of the toxin are considered mild, transient, and self-limited. However, the toxin technique is also prone to unfavorable outcomes and complications, just like any other injectable procedure. When the safety zones are respected, the chance of any of these complications is practically null.^[40]

It is generally agreed that single doses of Botox-A should not exceed 500 units.^[41] Understanding the area of treatment and the muscles corresponding to that area is essential to minimize the adverse effects. According to a study, it was showcased that the lateral limbus line, pupillary midline, eyelid lateral canthus, lateral orbital rim, and upper orbital rim are the safest areas for esthetic toxin treatment of the upper face.^[40] Attention to these areas and avoiding the danger zones are most likely to help prevent adverse effects.

Blepharoptosis which is one of the common complications can be managed by the administration of medications,

Complications with Botulinum Toxin Injection	
Injection reactions	
Anxiety or vasovagal episode	
Ecchymosis	
Erythema, edema, and tenderness	
Headache	
Infection	
Pain	
Paresthesia or dysesthesia	
Undesired botulinum toxin effects	
Allergic reaction	
Antibodies against botulinum toxin	
Blepharoptosis	
Eyebrow ptosis	
Distant spread from the injection site	
Facial asymmetry	
Medication interactions	
Undesired eyebrow shape or unsatisfactory result	

Figure 4: Complications of Botulinum toxin Injections.^[46]

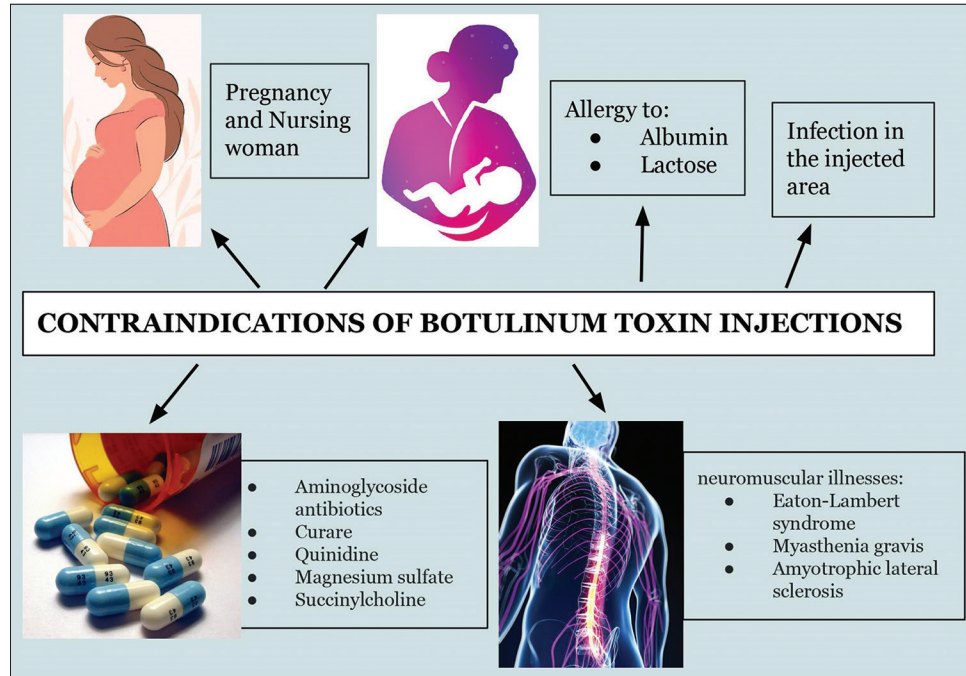


Figure 5: Contraindications of Botulinum toxin.

such as oxymetazoline hydrochloride or apraclonidine hydrochloride eye drops, anticholinesterase agents, or transdermal Botox-A injections to the pre-tarsal orbicularis, which can at least partially reverse eyelid ptosis.^[42]

A favorable side effect profile with minimal adverse effects reinforces that onabotulinumtoxin A is a safe and effective treatment option with a diverse portfolio of clinically accepted applications.^[43]

Contraindications

Patients who are hypersensitive to the ingredients in the formula should not receive the toxin treatment. Albumin and lactose are two of the ingredients. The toxin procedures should not be performed on pregnant or nursing women since they are contraindicated. Botox can increase neuromuscular illnesses such as Eaton-Lambert syndrome, myasthenia gravis, and amyotrophic lateral sclerosis, which can lead to severe muscle weakening and are contraindicated. The toxin treatments should not be performed on patients taking aminoglycoside antibiotics (gentamicin, streptomycin, amikacin, tobramycin, paramycin, netilmicin, spectinomycin) or other medications that affect neuromuscular transmission (non-depolarizing blockers such as curare, quinidine, magnesium sulfate, and succinylcholine)^[44] [Figure 5].

CONCLUSION

Botox is a neurotoxin drug that is widely used in the cosmetic industry. In a clinical setting, Botox A and Botox B are the only toxins used, the drug is typically safe, efficient, and has fewer side effects. Despite the latest procedures being more effective than the toxin, Botox is still a popular procedure that is increasingly becoming popular among men. Given its adverse benefits and varied usage, the demand for the toxin sees no setback in the constantly evolving cosmetic industry.

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Ethical approval

Ethical approval was not required for this study

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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