Chapter 5

# Botulinum Toxin

5

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## Core Messages

- *Clostridium botulinum* produces eight serologically distinct toxins: A, B, Cα, Cβ, D, E, F, G. Of the eight serotypes, A is the most potent.
- Botulinum toxin type A and type B are the only commercially available serotypes and are used for various medical indications, including cosmetic treatment.
- Botulinum toxin relaxes the underlying muscles of expression, leading to a reduction in the formation of skin creases. Over time, regular maintenance treatments can lead to the disappearance of these creases.
- Botulinum toxin is safe and effective in all skin types (Fitzpatrick I–VI).

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## 5.1 Introduction

The formation of crease lines and rhytids is a natural component of the aging process. As individuals enter their 30s and 40s, fine lines, creases, rhytids, and sagging skin become apparent, and deep furrows and frown/scowl lines often develop. Such furrows and frown/scowl lines are referred to as dynamic rhytids because they arise when we laugh, frown, or smile and are caused by the repeated forces generated by the underlying muscles. These hyperkinetic muscles include the frontalis (responsible for forehead furrows), corrugator supercilii (involved in frown/scowl lines), orbicularis oculi (responsible for crow's feet), and procerus and

depressor supercilii (also involved in frown/scowl lines). The repetitive contraction of these muscles beneath the skin causes creases and rhytids [1]. Botulinum toxin, a natural purified protein, is used to relax these facial muscles of expression.

## 5.2 Scientific Background



*Clostridium botulinum* (Fig. 5.1) produces eight serologically distinct botulinum toxins designated A, B, Cα, Cβ, D, E, F, G. Of the eight serotypes, A is the most potent, although serotypes B and F are almost as strong. These proteins are activated by complexing with hemagglutinin and the nontoxic molecule. A dimer forms, and activity is caused by the resulting inhibition of acetylcholine release from presynaptic neurons at the neuromuscular junction (NMJ). The inhibition takes place as the neurotoxin cleaves SNAP-25 proteins and ultimately leads to the chemical denervation at the motor end plate. Symptoms are characterized by striated muscle relaxation that usually begins 2–3 days after local injection. Relaxation is correlated with the amount of natural purified protein delivered. With exposure to increasing amounts, the relaxation may ultimately progress to total relaxation by 8–10 days postinjection. Although this process of chemical denervation is complete in all exposed NMJs, neurogenesis leads to recovery of the muscle in almost every situation. Denervation effects are generally inactivated in 3–6 months [1].

Botulinum toxin is an immunogenic protein and is capable of producing neutralizing and nonneutralizing antibodies. Treatment failure and eventual attenuation of the therapeutic effects may be traced to this immunogenic response. Fortunately, antibodies to one serotype of the botulinum protein do not cross-neutralize another, so an option for continuing therapy may be to change to another serological type [1]. For individuals treated for cosmesis or hyperhidrosis, the development of resistance has not been a problem. However, neutralizing antibodies have been reported in 3–5% of patients treated for dystonia [2, 3, 4].

### 5.2.1 Availability

Currently, four commercially available sources of the purified protein of botulinum toxin are available. Three sources contain type A: (1) Botox Medical and (2) Botox Cosmetic are available worldwide from Allergan (Irvine, CA, USA); (3) Dysport, from Speywood Pharmaceuticals (Spotsylvania, VA, USA), is available in many parts of the world but not currently in the United States. The fourth source, Myobloc, from Elan Pharmaceuticals (San Francisco, CA, USA) [5], contains botulinum toxin type B and is

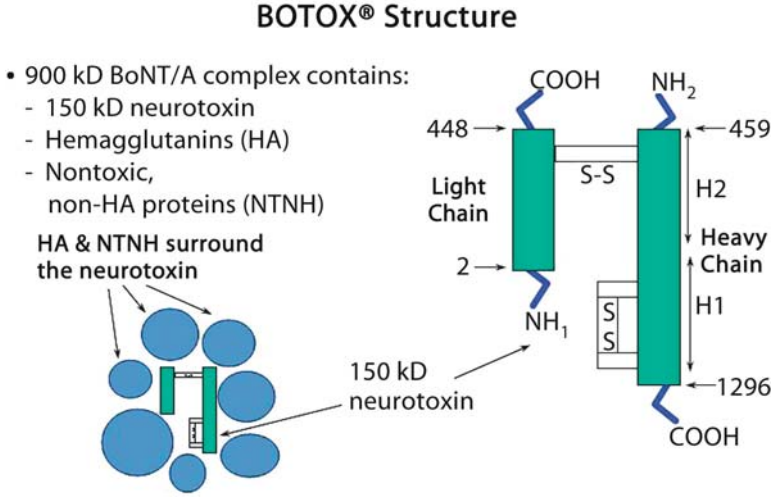


**Fig. 5.1.**
Chemical structure of botulinum toxin A

available under the name Neurobloc in Europe. Myobloc functions in a similar manner as the type A botulinum toxin, although the two serotypes are not interchangeable for all uses. Aside from being antigenically distinct serotypes, Myobloc differs from botulinum toxin type B in its formulation characteristics, complications, dosing, and response [5, 6].

### 5.2.2 History of Treatment Using Botulinum Toxin

Botulinum toxin type A has been used safely and effectively for more than 15 years to treat many disorders, including strabismus, blepharospasm, and myotonic dystrophies [1, 7]. The first evidence of potential therapeutic use was reported in 1973 when muscle relaxation was demonstrated in studies using a monkey model [8]. In 1980, the natural purified protein of botulinum toxin was used in the treatment of strabismus, marking the beginning of medical use of this molecule in human beings [1]. At present, botulinum toxin has been shown to be beneficial in the treatment of many disease states. A partial list of treatments is presented below.

#### 5.2.2.1 Partial List for the Use of Botulinum Toxin for Medical Purposes

The following list provides some of the medical applications for botulinum toxin [1]:

- Dystonia
- Cranial dystonia
- Blepharospasm
- Lower facial dystonia
- Oromandibular dystonia
- Cervical dystonia
- Spasmodic torticollis
- Craniocervical dystonia
- Meige's syndrome
- Laryngeal dystonia
- Spasmodic dysphonia
- Limb dystonia
- Sustained or fixed dystonia
- Task-specific dystonia
- Hemifacial spasm
- Tremor
- Tics
- Myoclonus, including palatal myoclonus
- Spasticity
- Multiple sclerosis
- Cerebral palsy
- Poststroke states
- Posttraumatic
- Ophthalmologic conditions
- Strabismus
- Acute oculomotor nerve palsy
- Nystagmus
- Masseteric hypertrophy
- Anal fissure
- Anismus
- Detrusor sphincter dyssynergia
- Achalasia
- Bilateral primary axillary hyperhidrosis [9]
- Brow furrows and frown lines

In 1991, Carruthers and Carruthers reported at the annual meeting of the American Society for Dermatologic Surgery the use of botulinum toxin injections for glabellar rhytids. In 1992, Borodic et al. noted a decrease in facial wrinkling in the course of treating individuals with

hemifacial spasm [10]. Such observations led to interest in botulinum toxin for treating rhytids. Since that time, additional research has been undertaken to explore its usefulness to treat hyperkinetic movement disorders as well as its capacity to reduce hyperkinetic glabellar facial lines. Numerous studies were undertaken in the mid-1990s; for example, one study evaluated the protein's ability to ameliorate facial kinetic frown lines [7] while a double-blind, placebo-controlled investigation evaluated its efficacy to treat glabellar folds [11]. A collaborative study of 210 injection sites in 162 patients showed the natural purified protein to be a safe and important adjunctive technique for the management of patients with symptomatic hyperfunctional facial lines [12].

Today, treatment of rhytids with botulinum toxin is the top nonsurgical procedure in the United States with over one million people injected. Demographics indicate that the volume of treatment will increase, as baby-boomer statistics reveal a large market with considerable financial assets: 78 million people aged 36–54 years old (born between 1946 and 1964). While only 29% of the US population, this segment controls 74% of personal financial assets (Allergan). This large market is driven by women in their 40s who have become self-aware of their aging, find that managing appearance is more urgent, and desire more than ever to take care of themselves (Fig. 5.2).

### 5.2.3 Muscles Involved in Treatment Using Botulinum Toxin

Tables 5.1, 5.2, and 5.3 and Figs. 5.3 and 5.4 depict the muscles involved in treatment with botulinum toxin [13].

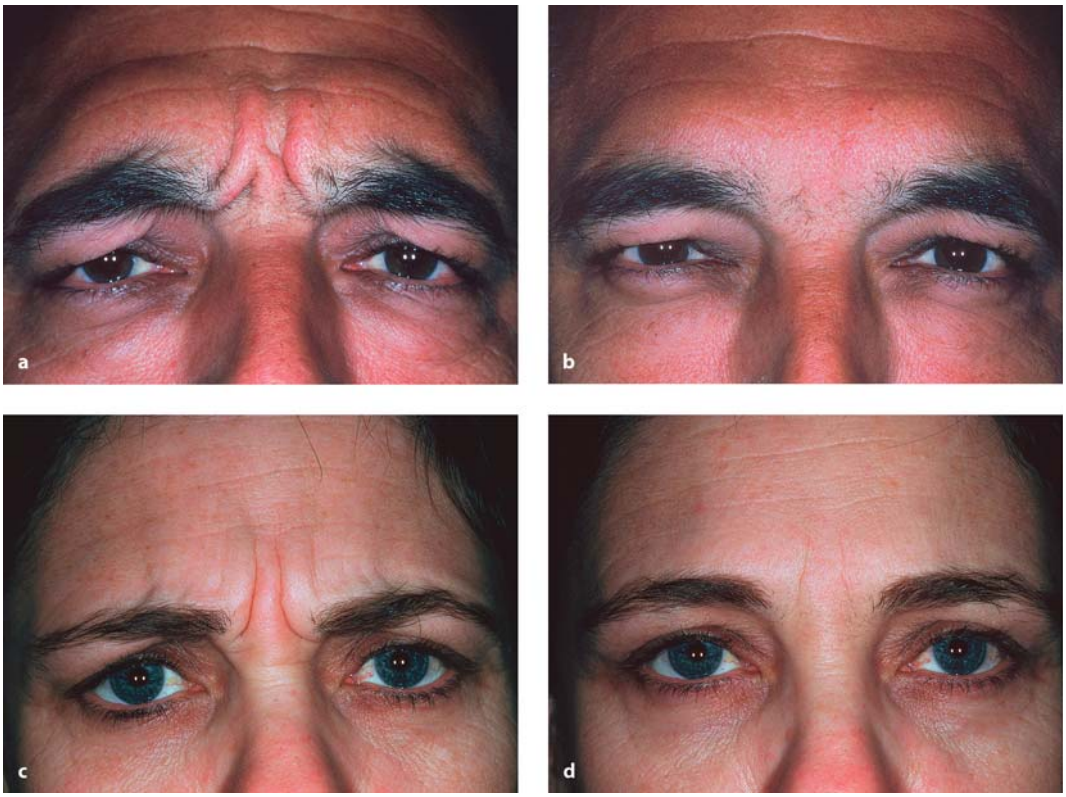


**Fig. 5.2.** Relaxation of the frown lines in a woman and man treated with Botox Cosmetic: before treatment and 4 weeks following treatment of the corrugator supercilii and procerus muscles

**Table 5.1.** Anatomic considerations: upper face

| Muscle | Function |
|---|---|
| Frontalis | Raises the eyebrows and produces transverse wrinkles of the forehead |
| Corrugator | Brings the eyebrows toward each other |
| Procerus | Pulls the glabellar skin in an inferior direction and causes a transverse rhytid |
| Depressor supercilii | Depresses the eyebrow |
| Orbicularis oculi | Functions as the sphincter of the eye |

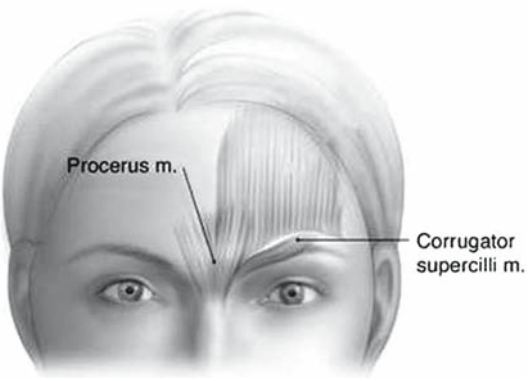


**Fig. 5.3.** Illustration of upper facial muscles involved in the expression of frowning

**Table 5.2.** Anatomic considerations: mid and lower face

| Muscle | Function |
|---|---|
| Risorius | Draws the corners of the mouth laterally |
| Orbicularis oris | Sphincter of the mouth |
| Levator labii superioris | Raises the upper lip |
| Depressor anguli oris | Depresses the corner of the mouth |
| Depressor labii inferioris | Lowers the lower lip |
| Modiolus | Wagon wheel of muscle situated just lateral to the external commissure of the mouth; the muscles of perioral and lip expression insert into here, allowing graded symmetrical perioral expression |

**Table 5.3.** Anatomic considerations: neck

| Muscle | Function |
|---|---|
| Platysma | Lowers the jaw and lip; tenses the neck; forms vertical bands and causes horizontal lines |

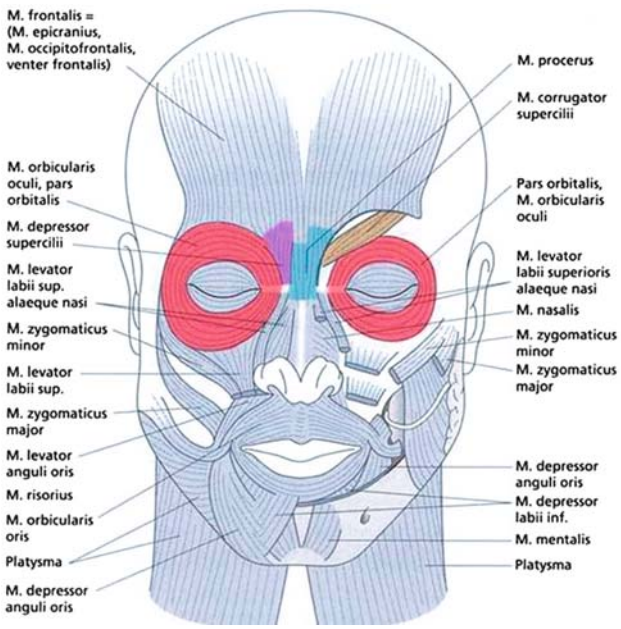


**Fig. 5.4.** Anatomic consideration of the face for the treatment with botulinum toxin A

## 5.3 Indications

### 5.3.1 Botulinum Toxin Type A

#### 5.3.1.1 Botox Medical

Botox Medical has the longest commercial history, having been approved by the FDA in 1989 for the treatment of strabismus and blepharospasm and in December 2000 for the treatment of cervical dystonia. Botox therapy is approved in over 70 countries for a broad range of conditions and is currently being investigated in the United States for even more medical conditions, among them hyperhidrosis [9], poststroke spasticity, back spasm, and headache [14].



#### 5.3.1.2 Botox Cosmetic

Botox Cosmetic was approved by the FDA in April 2002 for the temporary improvement in the appearance of moderate to severe glabellar lines in men and women 65 years of age or younger. While the approval specifically applies to the vertical lines between the eyebrows, there are numerous reports in the literature where other rhytids, such as crow's feet, horizontal forehead lines, neck lines, melolabial folds, and other hyperkinetic facial lines, have also been successfully treated [14, 15].

#### 5.3.1.3 Dysport

Dysport is another brand of botulinum toxin type A. It has been available in the United Kingdom since the early 1990s and has been used extensively there and elsewhere in Europe for a number of different medical indications, including blepharospasm, hemifacial spasm, and spasmodic torticollis [16]. Dysport is not currently approved for cosmetic use anywhere in the world. However, it is still favored by some practitioners in the United Kingdom as an alternative to Botox Medical for treating lines and rhytids.

### 5.3.2 Botulinum Toxin Type B

Myobloc contains botulinum toxin type B. It was licensed by the FDA in January 2001 for treatment of cervical dystonia. Elan Pharmaceuticals, the manufacturer of Myobloc, makes no recommendations for its use in cosmetic purposes. However, because it has FDA approval for treatment of cervical dystonia, patients in the United States can consent to off-label use for cosmetic purposes [17]. Moreover, the efficacy and safety of using botulinum toxin type B for cosmetic purposes has been demonstrated in a number of small pilot studies. Overall, the results of these studies found that botulinum toxin type B was an effective treatment for glabellar wrinkles [18, 19, 20, 21, 22, 23], forehead wrinkles [20, 21, 24], and crow's feet [21, 25, 26]. Further investigation of the safety and efficacy of using botulinum toxin type B for cosmetic purposes will be necessary.

## 5.4 Patient Selection

Today's aesthetically oriented consumer is ambitious, optimistic, and upbeat, placing great emphasis on a person's own beauty and seeking high levels of satisfaction with personal appearance. These consumers are also deliberate and thoughtful when considering methods to achieve satisfaction in appearance. However, qualitative research has found that individuals are not looking for dramatic work that brings drastic change because results are too obvious. The goal is to look better naturally, more well-rested, refreshed, and vital as well as less stressed, tired, and annoyed, which involves less frowning. Achieving a natural look, as if nothing has been done, brings self-confidence to patients.

### 5.4.1 Managing Patient Expectations

Cosmetic denervation with botulinum toxin is suitable for all skin types. It provides relaxation of dynamic rhytids giving patients a more youthful appearance. Deep furrows or rhytids may require higher doses and/or more yearly

treatments. Overall, doses will vary from person to person. It is important for patients to understand that they are not being paralyzed; rather, hyperkinetic muscles are being relaxed. They should also be made aware that Botox treatment does not improve the more common static rhytids that are unrelated to facial contraction. Moreover, cosmetic denervation will not improve loose or sagging skin and does not serve the same function as a facelift. For patients with a combination of dynamic and static rhytids, improvements may be limited if Botox treatment only is used. To optimize a treatment program, many options are available to use botulinum toxin in combination therapy, including injectable fillers and microimplants. Early results from clinical trials suggest that the duration of benefits from Botox treatment increases with time so that a patient may require less frequent injections in the future, but this varies from person to person.

### 5.4.2 Pretreatment Considerations

Because of the potential for bleeding, patients should avoid using (1) anticoagulants, including warfarin, aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDs); (2) nutritional supplements such as Ginkgo biloba, garlic, or vitamin E; and (3) alcohol.

### 5.4.3 Postinjection Considerations

Postinjection, patients may apply makeup even before leaving the physician's office. They should, however, avoid physical activity or exercise for the remainder of the day. If bruising becomes a concern, patients should immediately apply cold compresses to the injected area.

### 5.4.4 Contraindications

Botulinum injections are contraindicated in patients with a history of neurological disorders such as myasthenia gravis, amyotrophic lateral sclerosis, Eaton-Lambert syndrome, and myopathies [27, 28]. They are also contraindicated for individuals in the following categories:

- Pregnant or lactating women
- Psychological or medical contraindications
- Allergy to aminoglycoside antibiotics
- Infection at the proposed injection sites [14]

## 5.5 Treatment and Clinical Management

It is important to note that the definition of a unit of activity varies among Botox, Dysport, and Myobloc. In clinical use, Botox appears three to four times stronger (in mouse units) than Dysport, and the dose must be adjusted accordingly [15]. Determining an equivalent unit of Myobloc is more complicated due to differences in such details as the vehicle, dilution scheme, and laboratory protocols for various assays (Table 5.4) [29].

**Table 5.4.** Comparison of Botox and Myobloc preparations

| | Botox | Myobloc |
|---|---|---|
| Preparation | Lyophilized powder in vials of 100 U | Liquid in vials of 2,500, 5,000, and 10,000 U |
| pH | 7.2 | 5.5 |
| Complex size | 500–900 kDa | 500–700 kDa |
| Specific potency | 20 U/ng | 100 U/ng |
| Stability | Approximately 4 h after reconstitution | 2 years when stored at 4–8°C |
| Immunogenicity | Very low | Unknown |

### 5.5.1 Botulinum Toxin Type A

Botox Cosmetic is supplied in 100-U vials, which must be kept between 2°C and 8°C until used. Additionally, the sterile vacuum vial contains albumin and sodium chloride but does not contain a preservative. The 100-U vial is reconstituted with 2.5 ml of normal saline (0.9% NaCl), resulting in a final concentration of 4 U/cc of Botox Cosmetic. Due to the absence of a preservative, Botox Cosmetic should be stored in a refrigerator and used within 4 h. Small quantities are injected directly into the muscles to be treated (Table 5.5) using a 30- to 32-gauge needle and a calibrated syringe [14].

**Table 5.5.** Treatments and injection sites

| Region | Type of correction | Injection site | Additional Information |
|---|---|---|---|
| Facial asymmetry | Hemiparesis: naturally occurring or consequence of medical conditions such as Bell's palsy [30] | Contralateral muscles [30] | |
| Upper face | Glabellar creases | Corrugator/supercilli/ procerus | Orbicularis oculi: pretreatment snap test and Schirmer documented tear secretion |
| | Forehead lines | Frontalis | |
| | Forehead and brow shaping | Frontalis, depressor supercilii, lateral orbicularis oculi | |
| | Periorbital rhytids or crow's feet | Inferior ciliary margin of the orbicularis oculi [31] | |
| | Eye shaping to increase the palpebral aperture | | |
| Midface [32] | Nasalar radix (bunny lines), nasolabial folds | Levator alaeque nasi Levator labii superioris | Causes upper lip ptosis |
| | Nasal flare | | |
| | Gummy/canine smile | | |
| Lower face [32] | Marionette lines or mouth frown | Depressor anguli oris | Potential side effect includes asymmetric relaxation of the oral commissure |
| | Perioral rhytids and mouth shaping | Orbicularis oris | |
| | Peau d'orange (pebbly chin) | Depressor labii inferioris | |
| | | Mentalis muscle | |
| Neck [32] | Horizontal neck creases | Intradermal along the transverse neckline | Possibility of dysphagia |
| | Platysmal bands | Platysma | |
| Below the neck | Décolleté creases [33] | Subcutaneous muscle fibers running over the third intercostal spaces and over the presternal area [33] | |
| | Breast lifts | | |

The injections may cause some discomfort manifested as mild stinging or burning. Patients should avoid physical activity or exercise for the remainder of the day.

### 5.5.2 Botulinum Toxin Type B

Myobloc is sold as a premixed solution, ready to use, and it has a longer shelf life than Botox, maintaining its potency for many months stored at room temperature. Myobloc may serve as an alternative to patients who are resistant to botulinum toxin type A [6].

## 5.6 Complications/Adverse Reactions

Side effects most often reported during clinical trials included headache, respiratory infection, blepharoptosis, nausea, and flu syndrome. Less frequently occurring adverse reactions included pain in the face and erythema at the injection site. In rare cases, botulinum injections have caused transient relaxation of injected or nearby muscles, resulting in blepharoptosis (eyelid ptosis) or asymmetry of facial expression. Blepharoptosis is a short-lived side effect that can be reversed by treating with an alpha-1-adronergic agent. Asymmetry of facial expression can be corrected by relaxing the contralateral muscles. Unlike blepharoptosis, asymmetry of facial expression can be a prolonged side effect. The risk of any side effects depends on which muscles are injected. Because treatment is completely reversible, side effects related to excessive relaxation are temporary, lasting only days or weeks [14]. The human median lethal dose ($LD_{50}$) is estimated to be 40 U/kg (2,800 U for an average 70-kg individual) [34].

### 5.6.1 Other Reported Side Effects

Other side effects reported with botulinum toxin treatments are:

- Dry mouth
- Change in voice (platysmal/neck injections)
- Diplopia/blurred vision
- Ectropion
- Dry eyes
- Lymphedema
- Cheek ptosis
- Rash
- Abnormalities of cardiovascular reflexes
- Generalized weakness
- Muscle jitters [35, 36] (no clinical relevance)
- Ecchymosis, headache, muscle soreness–general areas, especially with glabella and forehead injections
- Upper eyelid to ptosis–glabellar injections
- Perioral dysfunction–perioral lines
- Potentiation of neurological disease
- Unresponsiveness to botulinum natural purified protein

## 5.7 Prognosis/Outcome

The effects of botulinum toxin relaxation of the underlying muscles of expression can last 3–5 months, and benefit increases over time, leading to a reduction in the formation of skin creases. If regular maintenance sessions achieve persistent muscle relaxation, these skin creases can diminish over time. However, regular maintenance sessions must take place before muscle relaxations completely reverse themselves.

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