Botulinum Toxins
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Cosmetic and Clinical Applications

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Contents

List of Contributors vii
About the Companion Website xiii
Video Table of Contents xv
Foreword: Botulinum Toxins in Dermatology xvii

1 History of Botulinum Toxin for Medical and Aesthetic Use 1
Alastair Carruthers, FRCP and Jean Carruthers, MD (FRCS(C), FRCOphth)

2 Anatomy and Aesthetic Principles 13
Timothy M. Greco, MD (FACS), Chérie M. Ditre, MD, and David M. Ozog, MD (FAAD, FACMS)

3 Botulinum Toxin: From Molecule to Medicine 37
Conor J. Gallagher, PhD and Alan Ackerman, PhD

4 Myobloc 53
Neil S. Sadick, MD (FACP, FAAD, FAACS, FACPh) and Suveena Manhas-Bhutani, MD

5 Abobotulinumtoxin: Development and Aesthetic Usage 65
Gary D. Monheit, MD

6 IncobotulinumtoxinA (Xeomin®/Bocouture®) 79
Ulrich Kühne, MD (DALM) and Matthias Imhof, MD (DALM)

7 Future Injectable Toxins 97
Michael H. Gold, MD

8 Reconstitution, Dilution, Diffusion, and Migration of Botulinum Toxin 109
Murad Alam, MD (MSCI, MBA), Hayes B. Gladstone, MD, and David M. Ozog, MD (FAAD, FACMS)

9 Patient Selection 121
Ryan M. Greene, MD (PhD, FACS), John P. Arkins, BS, and Steven H. Dayan, MD (FACS)

10 Treatment of the Glabella 133
Neal D. Varughese, MD (MBA) and David J. Goldberg, MD (JD)

11 Treatment of the Forehead 147
Joel L. Cohen, MD (FAAD, FACMS) and Ramin Fathi, MD
12 Treatment of the Periocular Area – Crow’s Feet, Brow, and Bunny Lines  165
Girish S. Munavalli, MD (MHS, FACMS), Anthony V. Benedetto, DO (FACP, FCPP),
Brian S. Biesman, MD (FACS), and Carolee M. Cutler Peck, MD

13 Contouring of the Lower Face and of the Lower Leg and Calf  177
Mee young Park, MD (PhD), Dennis A. Porto, MD, and Ki Young Ahn, MD (PhD)

14 Treatment of the Perioral Area  191
Shawn Allen, MD (FAAD, FACMS), Roberta Sengelmann, MD, and Rachel Simmons, MD (FAAD)

15 Neck Rejuvenation  199
Koenraad De Boulle, MD, Lakhdar Belhaouari, MD, and Julia D. Kreger, MD

16 Correction of Facial Asymmetry  213
Scott Rickert, MD (FACS), Lesley F. Childs, MD, and Andrew Blitzer, MD (DDS, FACS)

17 Complications and Diffusion  221
Matteo C. LoPiccolo, MD, Farhaad R. Riyaz, MD, and David M. Ozog, MD (FAAD, FACMS)

18 Combination Therapy of Botulinum Toxin with other Nonsurgical Procedures  233
Amy Forman Taub, MD and Lauren Fine, MD (FAAD)

19 Peri-Procedural Botulinum Toxin for Skin Cancer Patients and Scars  253
Timothy Corcoran Flynn, MD, Molly C. Powers, MD, and David M. Ozog, MD (FAAD, FACMS)

20 Achieving a Natural Look  263
Dóris Hexsel, MD, Camile L. Hexsel, MD (FAAD, FACMS), and Carolina Siega, BSc

21 Special Considerations in Darker Skin  275
Cheré Lucas Anthony, MD and Marta I. Rendon, MD (FAAD, FACP)

22 Axillary Hyperhidrosis  285
Ada Regina Trindade de Almeida, MD, Joel L. Cohen, MD (FAAD, FACMS),
and Chinobu Chisaki, MD

23 Primary Focal Palm, Sole, Craniofacial, and Compensatory Hyperhidrosis  299
Dee Anna Glaser, MD and Adam R. Mattox, DO (MS)

24 Topical Botulinum Toxin  317
Richard G. Glogau, MD and Eileen Axibal, MD

25 Exciting New Uses of Botulinum Toxin Type A: Dermatology/Dermatologic Surgery and Beyond  329
Donna Bilu Martin, MD (FAAD) and Stephen Mandy, MD (FAAD)

26 Modulating Affect and Mood with Botulinum Toxin Injections: Psychosocial Implications of Neuromodulators  345
James L. Griffith, MD (MSci), Kevin C. Smith, MD (FRCP (DERM)), and Murad Alam,
MD (MSCI, MBA)

27 OnabotulinumtoxinA (Botox®) in Dermatology  357
Jason J. Emer, MD, Eileen Axibal, MD, Ellen S. Marmur, MD (FAAD), and Heidi Waldorf, MD

Index  369
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About the Companion Website

Don’t forget to visit the companion website for this book:

www.wiley.com/go/cohen/botulinum

This site hosts valuable video materials to enhance your learning:

Dr Cohen and Dr Ozog present several patient cases, focusing on patient evaluation, preparation for toxins, and specific injection techniques. Each patient is appraised carefully and optimal injection techniques are discussed, along with methods for avoiding adverse effects, and ways to minimize injection points and related bruising. One week follow up videos will highlight optimization of results.
Video Table of Contents

1. Introduction from Dr Joel L. Cohen and Dr David M. Ozog
2. Discussion on reconstitution techniques from Dr Joel L. Cohen and Dr David M. Ozog

Patient Cases

Patient 1, 66-year old female, *Dr Joel L. Cohen, Dr David M. Ozog*
   a) Evaluation
   b) Glabellar Complex
   c) Lateral Canthal Area
   d) One Week Follow Up

Patient 2, 43-year old female, *Dr Joel L. Cohen, Dr David M. Ozog*
   a) Evaluation
   b) Forehead
   c) Glabellar Complex
   d) Lateral Canthal Area
   e) One Week Follow Up

Patient 3, 69-year old female, *Dr Joel L. Cohen, Dr David M. Ozog*
   a) Evaluation
   b) Glabellar Complex
   c) Lateral Canthal and Infraorbital Area
   d) One Week Follow Up

Patient 4, 48-year old female, *Dr Joel L. Cohen, Dr David M. Ozog*
   a) Evaluation
   b) Glabellar Complex
   c) Lateral Canthal Area
   d) One Week Follow Up

Patient 5, 72-year old female, *Dr Joel L. Cohen, Dr David M. Ozog*
   a) Evaluation
   b) Glabellar Complex
   c) Lateral Canthal Area
   d) One Week Follow Up

Patient 6, Treatment of Platysmal Bands in female, *Dr Koen De Boulle (narrated by Dr Dennis A. Porto)*
   a) Depressor Septi Nasi
   b) Mentalis and Depressor Anguli Oris
   c) Platysmal Bands
   d) One Week Follow Up for Platysmal Bands

Patient 7, *Dr David M. Ozog*
   a) Depressor Septi Nasi
   b) Mentalis and Depressor Anguli Oris
   c) Platysmal Bands
   d) One Week Follow Up for Platysmal Bands

Patient 8, Treatment of Lower Face and Neck in 63-year old female patient, *Dr Gary D. Monheit (narrated by Dr Dennis A. Porto)*
   a) Evaluation
   b) Glabellar Complex
   c) Lateral Canthal and Infraorbital Area
   d) One Week Follow Up
Foreword: Botulinum Toxins in Dermatology

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\textit{Clostridium botulinum (C. botulinum)}, discovered over a century ago as the bacterium responsible for botulism, has risen through medical ranks to become the basis of what is one of the most requested procedures in facial rejuvenation and accepted therapeutic options for use in a variety of clinical scenarios.

Until the 1980s, botulinum toxin (BoNT) was merely a potent toxin with devastating effects and up to a 65\% mortality rate. The history of food-borne illness to therapeutic agent is checkered with tainted blood sausages, brilliant clinical scientists, biological warfare and, at the heart of it all, an understanding that this toxin that led to so many deaths and devastated the canning industry in the 1930s, could somehow be of clinical use.

Interestingly, the clinical use of BoNT has proven circular: its initial forays into therapeutics, as a nonsurgical treatment for strabismus and blepharospasm, sparked discoveries in facial rejuvenation; the enormous acceptance of its cosmetic use has in turn fuelled the expansion and tremendous growth in therapeutic fields, leading to an even greater clinical experience and understanding of mechanism of action and potential indications for use.

In the last 5 years, the use of BoNT has grown exponentially and now accounts for about half (along with soft-tissue augmenting agents) of all nonsurgical cosmetic procedures in North America. The reasons for such an enthusiastic response to the toxin may be found in the target populations. As we age, the skin atrophies and sags, bones shift, and lines and wrinkles become more prominent. Ameliorating those wrinkles is one of the primary methods of turning back the clock. The fact that BoNT is able to accomplish this feat with minimal downtime or side effects has contributed greatly to its rise in popularity. Moreover, BoNT may be considered a preventative anti-aging modality, appealing to a younger population in addition to those seeking to eradicate already established rhytides and folds.

Therapeutically, indications for BoNT have progressed beyond movement disorders and spasticity to investigations into potential uses for a multitude of disorders and syndromes, including those involving pain, the endocrine system (sweat, lacrimal, and salivary glands), and the central nervous system, among others. Clinicians from nearly all therapeutic specialists have turned their attention, at least in part, to possible applications of BoNT.

It is becoming more difficult to stay abreast of new developments. This book has been compiled to highlight not only the
remarkable history and clinical advance of what was once called "sausage poison, but to include the ever-expanding indications, along with a number of new formulations available and the associated side effects or complications. There is a detailed examination of facial anatomy and BoNT in the upper, mid- and lower face and neck, with additional focus on the more artful role of the toxin's ability to restore symmetry and sculpt the face into more pleasing contours, both alone and in combination with other agents and surgical procedures. Patient considerations are of equal importance, both in choosing the most appropriate candidates, and in predicting outcomes. Evidence shows that BoNT has enormous psychosocial impact in the lives of our patients. This book also includes dermatological BoNT outlying the cosmetic domain, such as benefits of using the neurotoxin to treat hyperhidrosis, skin cancer and traumatic scars, and in conjunction with surgical procedures to aid in wound healing or prolong the aesthetic effect.

A book on the dermatological applications of neurotoxin would not be complete without inclusion of the exciting possibilities. Since its clinical properties were discovered nearly a century ago, it is clear that we have not yet uncovered the full potential of what still is the world's most lethal toxin.

Dr. Joel Cohen has achieved an outstanding international reputation both among his colleagues and his patients. He went to medical school at Mt Sinai School of Medicine, New York and then did his dermatology training at Henry Ford Hospital, Detroit. That was followed by a fellowship in advanced dermatologic surgery in Vancouver, B.C. which is where we first met Joel and his family.

Since he completed his training, Dr. Cohen has appeared in the national media on many occasions and has published extensively in the medical literature. Much of this relates to his interest in botulinum toxin and its use in dermatology. His knowledge in this area as well as his contributions to the field are both extensive and these have contributed to his excellent reputation.

Dr. David Ozog trained in medicine at the University of Rochester, N.Y., did his dermatology residency at Henry Ford Hospital in Detroit and his Mohs and cosmetic surgery fellowship with Dr Ron Moy in Beverly Hills, CA. He remained in academics at Henry Ford as Chairman and Director of Cosmetic Dermatology, where he has been teaching residents both surgery and cosmetics for the past thirteen years. An excellent background! He has proven himself to be an excellent teacher and to have an inquiring mind – both valuable attributes.

It is very appropriate that they edit this book which brings together both their own knowledge as well as that of other experts in the field under their direction. This book is an important contribution to our knowledge about both the basic science and the clinical use of botulinum toxin.

Reference

Sausage Poisoning

In the late 1700s in Europe, outbreaks of a deadly illness from contaminated foods swept across the continent, fueled in part by the poverty from the Napoleonic War (1795–1815) that led to unsanitary food production [1]. The primary source of food-borne illness of the time: smoked blood sausages. One of the biggest outbreaks occurred in 1793 in Wildebrad, Southern Germany; by 1811, the Department of Internal Affairs of the Kingdom of Württemberg named “prus-sic acid” as the culprit in sausage poisoning [2]. Intrigued, the district medical officer and poet, Dr. Justinus “Würst” Kerner (1786–1862), began what would become a lifelong quest to uncover the mysteries of the poison. He would later be considered the godfather of botulinum toxin (BoNT) research for his early, intensive work. In 1817 and 1820, Kerner identified and described the first accurate descriptions of botulism (a term coined in 1871 from the Latin botu-lus, meaning “sausage”) [2, 3]. In 1822, he compared contaminated sausage ingredients and concluded that the toxin must occur in fat, leading him to call the suspicious substance “sausage poison,” “fat poison,” or “fatty acid,” and published the first complete monograph of the “fatty toxin” from blood sausages [2].

In his monograph, Kerner described the symptoms of botulism – including vomiting, intestinal spasms, mydriasis, ptosis, dysphagia, and respiratory failure – and recommended methods for the treatment and prevention of food poisoning. Through animal and self-experimentation, Kerner observed that the toxin developed under anaerobic conditions and was lethal in small doses. Since the effects of this blood poison were similar to atropine, scopolamine, nicotine, and snake venom, Kerner surmised that sausage poison was likely biological in nature – remarkable in that microscopic pathogens had not yet been discovered at that time – and interrupted signal transmissions within the peripheral and autonomic nervous system. Indeed, some would call Kerner prophetic: he suggested that small amounts of this sausage poison might be used to lower sympathetic nervous system activity associated with movement disorders (i.e., treat St. Vitus’ dance or Sydenham’s chorea, a disorder characterized by jerky, uncontrollable movements, either of the face or of the arms and legs) and hypersecretion of bodily fluid, as well as to treat ulcers, delusions, rabies, plague, tuberculosis, and yellow fever [4].
Identification of C. botulinum

Microbiologist Professor Emile Pierre van Ermengem (1851–1922) trained under Robert Koch, who discovered anthrax, tuberculosis, and cholera and was the first researcher to prove that microorganisms could cause disease in animals [5]. In 1897, Van Ermengem identified the bacterium Clostridium botulinum (originally called Bacillus botulinus) as the causative agent of botulism after examining postmortem tissue of patients in Belgium who had contracted gastroenteritis and died from eating raw, salted pork [6]. Over the next twenty years, different strains of the bacterium that produced serologically distinct types of toxins were recognized; these were eventually classified alphabetically into seven serotypes (A, B, C1, D, E, F and G) [7]. In 1928, Dr. Herman Sommer (University of California, San Francisco) isolated the most potent serotype – BoNT type A (BoNTA) – in purified form as a stable acid precipitate, paving the way for future studies [8].

Biological Weapon of Warfare

During the First World War, Germany unsuccessfully attempted to produce chemical and biological weapons. As World War II approached, the American government learned that multiple countries were engaged in bio-warfare programs. In response, and on orders from President Franklin Roosevelt, the US National Academy of Sciences and Fred Ira Baldwin, chairman of the bacteriology department of the University of Wisconsin, gathered bacteriologists and physicians in a laboratory named Fort Detrick (Maryland). The purpose of Fort Detrick: the investigation of dangerous infectious bacteria and toxins to use as offensive and defensive biological weapons [1].

In 1946, Carl Lamanna and James Duff developed concentration and crystallization techniques for the toxin that were subsequently used by Dr. Edward J. Schantz, a young US army officer stationed at Fort Detrick to produce the first BoNTA lot for human use (the basis of the later clinical product) [9, 10]. The US Office of Strategic Services (OSS) developed a plan using Chinese prostitutes to assassinate high-ranking Japanese officials via gelatin capsules containing the newly purified BoNTA. The government abandoned the plan when test donkeys that received the capsules survived [1]. Ironically, though BoNT today is considered one of the deadliest poisons in the world – 1 g has the potential to kill 1 million people – the toxin is not an ideal biological weapon, since large amounts must be ingested and mortality rates vary).

In 1972, President Richard Nixon signed the Biological and Toxic Weapons Convention, effectively putting an end to all investigations on biological agents for use in war. Schantz took his research to the University of Wisconsin, where he produced a large amount of BoNTA (batch 79–11) that remained in clinical use until December of 1997 [11].

Human Experimentation

Clinical use of the toxin began in the late 1960s and early 1970s, when Dr. Alan Scott (Smith-Kettlewell Eye Research Foundation, San Francisco; Figure 1.1) began experimenting with BoNTA, supplied by Dr. Schantz, and other chemical agents in monkeys, with the hope that one of the compounds could be used for the nonsurgical treatment of strabismus in humans [12, 13]. Scott published his first primate studies proving that BoNTA could weaken extraocular muscles in 1973, and postulated that the toxin could be used for a wide variety of musculoskeletal disorders and spasticity, even before conducting any human studies [13, 14]. In 1978, Scott received Food and Drug Association (FDA) approval to begin testing small amounts of the toxin (then named Oculinum) in human volunteers; his landmark paper, published in 1980 [15], showed that intramuscular injections of BoNTA could correct gaze...
1 History of Botulinum Toxin for Medical and Aesthetic Use

misalignment in humans. In 1989, one year after manufacturer Allergan Inc. (Irvine, CA) acquired the rights to distribute Scott’s Oculinum in the United States, BoNTA was approved for the nonsurgical correction of strabismus, blepharospasm, hemifacial spasm, and Meige’s syndrome in adults, and clinical use expanded to include the treatment of cervical dystonia and spasmodic torticollis [13, 16, 17]. Shortly thereafter, Allergan bought Scott’s company and renamed the toxin. Botox® was born.

The Cosmetic Connection

In the mid-1980s, Dr. Jean Carruthers, an ophthalmologist in Vancouver, Canada, noticed that her patients injected with BoNTA for blepharospasm experienced a reduction in glabellar rhytides, and discussed the findings with both Scott and her dermatologist spouse, Dr. Alastair Carruthers, who was attempting to soften the forehead wrinkles of his patients using soft-tissue augmenting agents available at that time. Intrigued by the possibilities, the Carruthers used the toxin experimentally in their receptionist’s forehead and subsequently published the first report of BoNTA for the treatment of glabellar frown lines in 1992 [18] (Figure 1.2). Other reports soon followed [19, 20], including the first double-blind, placebo-controlled study for the treatment of hyperkinetic facial lines [21].

Properties, Mechanism of Action, and Clinical Effect

Clostridium botulinum is a rod-shaped, gram-positive anaerobic bacterium. Of the seven serotypes, A, B, and E are commonly involved in human botulism [22]. BoNT is a high-molecular-weight protein of 150,000 daltons with nonconvalent proteins protecting it from digestive enzymes, making it a lethal cause of food poisoning [1]. The symptoms of botulism include disturbances in vision, speech, and swallowing, with asphyxia and death sometimes occurring 18–36 hours after ingestion (mortality rate: 10–65%) [22].

Researchers gained an understanding of mechanism of action in the late 1940s, when they discovered that BoNT blocks neurotransmitter release at the neuromuscular junction [23]. The follow-up discovery in the mid-1950s that BoNT blocks the release of acetylcholine from motor nerve endings when injected into hyperactive muscles led to a renewed interest in the neurotoxin as a potential therapeutic agent [3].

Although all seven serotypes block neuromuscular motor transmission by binding to receptor sites on motor nerve terminals and inhibiting the release of acetylcholine, producing temporary chemodenervation of the muscles, each differs with regard to cellular mechanism of action and clinical profile [24, 25]. The commercially available subtypes – type A (BoNTA) and type B (BoNTB) – are both 150 kDa dichain polypeptides.
Botulinum Toxins

Figure 1.2 The Carruthers’ first patient treated in the glabella area for cosmetic reasons alone. Seen (a) before frowning; (b) after frowning; (c) before at rest; (d) after at rest.

comprising heavy and light chains linked by disulfide bonds. The light chain of BoNTA cleaves to a 25 kDa synaptosomal associated protein (SNAP-25), a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings, while the light chain of BoNTB cleaves to vesicle-associated membrane protein (VAMP or synaptobrevin). This difference may be responsible for some of the differences witnessed in the clinical effect of the subtypes [12]. When injected intramuscularly at therapeutic doses, BoNT produces temporary chemical denervation of the muscle, resulting in a localized reduction of muscle activity. The process of cellular recovery after injection of BoNT is only partially understood. Initial recovery of muscle contraction is accompanied by collateral sprouting of active terminal buds near the parent terminal. However, research indicates that these new sprouts are only transitory; neurotransmission is eventually restored at the original nerve ending, accompanied by the elimination of the dispensable sprouts [26], suggesting that treatment with BoNT does not permanently alter the neuromuscular junction. Recommended doses of injected neurotoxin do not result in systemic clinical effects in patients without other neuromuscular dysfunction. Studies of human and animal tissue show that in the first 2 weeks postinjection with BoNTA, the target muscle begins to atrophy, with changes in individual muscle fibers [27]. The paralytic effect of the toxin is dose-related, with initial effects occurring within 2–3 days and peaking approximately 1–2 weeks after treatment [28]. Atrophy continues for approximately 4 weeks before stabilizing; clinical recovery of function occurs 3–6 months posttreatment [29]. There is an area of denervation associated with each point of injection due to toxin spread of about 1–1.5 cm (diameter, 2–3 cm). Repeated injections can extend the clinical effect for up to 12 months [29]; it is possible
that over the course of treatment, individuals alter their habitual use of muscles that cause expression lines. Long-term remodeling of the dermis and epidermis that helps to sustain the cosmetic effects also occurs in most individuals, because the tissue is no longer subjected to the same forces of muscle contraction.

A Multitude of Formulations

Until recently, one product – at least for cosmetic purposes – dominated the market: onabotulinumtoxinA (Botox®/Botox Cosmetic®/Vistabel®/Vistabex®; Allergan, Inc., Irvine, CA). Now, however, a host of other agents have joined the original formulation to fight the signs of aging. Of the formulations of BoNTA available or in development, the original, onabotulinumtoxinA, is the most recognized and discussed in peer-reviewed literature. Botox Cosmetic, which was approved by the US FDA in 2002 for the treatment of glabellar rhytides [30], has gone on to receive approval for 20 indications in more than 75 countries [31]. Now three formulations of botulinumtoxin type A are approved for cosmetic use in North America. The original onabotulinumtoxin A has been joined by abobotulinumtoxinA (Dysport®) and IncobotulinumtoxinA (Xeomin®). Initially approved in over 65 countries for therapeutic indications (Dysport®; Ipsen Ltd., United Kingdom/Medicis, Scottsdale, AZ; and Azzalure® in 15 European countries; Galderma, France), abobotulinumtoxinA received FDA approval for cosmetic applications in North America in 2009 (Dysport®; Ipsen Ltd). Although produced from the same serotype, abobotulinumtoxinA differs from onabotulinumtoxinA in purification procedures, dosing, injection schedules, and clinical effect [32]. Units of abobotulinumtoxinA are less powerful than those of onabotulinumtoxinA; most cosmetic injectors use a multiple of two to three times the number of units. Overall, abobotulinumtoxinA is safe and well tolerated [33, 34]. A third BoNTA (Xeomin®/NT-201; Merz Pharmaceuticals, Frankfurt, Germany) is approved for therapeutic indications in Germany and other European countries, the United States, Canada, Mexico, and Argentina, and has been approved for the treatment of glabellar rhytides in Argentina and the United States. Clinically, Xeomin and onabotulinumtoxinA appear to behave in a similar fashion, with equal levels of potency, safety, and duration of effect [35–40]. Xeomin is free of complexing proteins, which some believe may result in purer formulations with greater efficacy and a reduced risk of sensitization and antibody formation [37]. One formulation of BoNT type B (BoNTB) is also available in North America. RimabotulinumtoxinB (Myobloc®/NeuroBloc®; Solstice Neurosciences Inc./Eisai Co., Ltd.) was FDA-approved in 2000 for the treatment of cervical dystonia but has been used off-label to treat facial wrinkles with some success [41–44]. BoNTB works faster than but does not last as long as BoNTA [45], although duration has been shown to be dose dependent [46]. BoNTB tends to diffuse more widely than BoNTA and injections can be more painful and may lead to additional side effects [45]; however, a close examination of several doses found all to be safe and effective for cosmetic use [46].

Cosmetic Applications

Hyperkinetic lines result from the repeated contraction of muscles perpendicular to the wrinkles. Weakening or relaxing these muscles with BoNTA can smooth these lines, including horizontal lines on the forehead (from frontalis contraction), vertical lines in the glabellar region between the eyebrows (caused by the corrugator muscles), horizontal creases across the bridge of the nose (from procerus contraction), “crow’s feet” and lateral lines along the lower eyelid (caused by contraction of the lateral orbicularis oculi), and perioral lines (from contraction of the orbicularis oris). Deep grooves or folds
Facial Sculping

Facial rejuvenation with BoNT has expanded to involve a more artistic shaping and sculpting of the face. Now, in addition to targeting simple dynamic rhytides, careful injection of the toxin can be used to lift and shape the brow [53], widen the eyes [12, 54], correct facial asymmetry due to nerve palsies [55], dystonias [17, 20], surgery [56], or trauma [57], and to reduce muscle thickness of the jaw in patients with masseteric hypertrophy (Figure 1.3) [58–61].

Adjunctive Therapy

BoNT is used increasingly in combination with other facial rejuvenation procedures, such as soft-tissue augmentation [28, 62–66] and laser or light-based therapies [12, 28, 67–71], particularly for the treatment of deeper, more static rhytides and folds. BoNT is also used during surgery to prolong or enhance the aesthetic results and as an aid in wound healing and minimizing scars (Figure 1.4) [12, 73–77].
Therapeutic Applications

Intramuscular injections of BoNTA have become the treatment of choice for a number of disorders characterized by muscular hyperactivity, such as strabismus [15], blepharospasm and hemifacial spasm [17], cervical dystonia [78], focal dystonia (writer’s cramp) [79], and spasticity due to stroke [80, 81], and cerebral palsy [82]. In addition, the ability of BoNT to block acetylcholine release from autonomic nerve endings innervating glandular tissue or smooth muscle has led to investigation of its use for other indications, including Frey’s syndrome [83] and hyperhidrosis [84–89], as well as various gastrointestinal, genitourinary, and sphincter disorders [90], dyshidrotic hand eczema [91, 92], and allergic rhinitis [93, 94]. Flushing of the face and chest can be successfully treated with BoNT due to its ability to regulate blood vessel constriction [95, 96]. Clinicians continue to investigate the use of BoNT for the treatment of chronic pain disorders, including chronic lumbar [97], temporomandibular dysfunction [98], myofascial [99], and neuropathic pain [100], although the toxin’s efficacy in the treatment of headache disorders is under debate [101]. More recent research includes applications of BoNT to relieve the pain of arthritis [102, 103].

Future Directions

It is interesting to note that what once began as a potential – rather daring – treatment for a single disorder has translated into a worldwide phenomenon. And one cannot help but wonder what Justinus Kerner would think of his “sausage poison” now that so consumed his time and became his life’s research. BoNT has become the treatment of choice for smoothing hyperkinetic lines and shaping the face, alone or in combination with other rejuvenating procedures. Therapeutic applications include a variety of movement, pain, autonomic nervous system, and gastrointestinal and genitourinary disorders, among others. Current recruitment for clinical trials includes everything from arthritis and clubfoot to acne and depression, with new products emerging or on the horizon. Indeed, BoNT seems to have invaded nearly every aspect of clinical medicine, at least in some way, and there is no doubt that the range of indications will only continue to expand.

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Anatomy and Aesthetic Principles

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Anatomy of Youthful versus Aging Skin

Apparent age is readily judged by several factors including the presence and numbers of facial wrinkles, dyschromia, and skin laxity among other anatomic aging skin changes. To understand treatment with neuromodulators, it is important for the reader to familiarize themselves with basic facial skin anatomy as well the anatomy of aging skin and its underlying structures. The neurotoxin injector can then precisely target the intended underlying muscles being treated with an understanding of the expected improvement from the toxin as well as the potential need for adjuvant therapies.

Youthful skin is characteristically smooth in texture, having a dewy luster, even tone, high elasticity, and pleasant balanced contours due to appropriate tissue volume. Rhytides are absent or minimal at rest. Youthful skin is by definition, normal or unaltered in anatomical configuration and histology.

Aging skin, in contrast, exhibits surface irregularities such as textural roughness, tautness, pigment alterations, and inelasticity as well as the appearance of wrinkles/rhytids. In addition, subsurface changes, namely loss of volume due to dermal atrophy, fat atrophy and redistribution, and biometric volume loss due to deeper compartmental changes such as bony and cartilaginous resorption, ensue. Aging skin is viewed as an alteration of the skin's normal anatomy.

Wrinkles themselves are one modification of the aging process, but nevertheless are typically the most characteristic hallmark. Despite this, there are few studies dedicated to defining wrinkles both clinically and histologically. These factors have muddied the anatomic and histologic definition of wrinkles.

Kligman attempted to define wrinkles by histologic examination of 58 patients with a variety of wrinkle types from the cheeks, crow’s feet, temporal frown lines, upper vertical lip lines and other body areas of wrinkling skin such as the abdomen and the back of the neck. He concluded that wrinkles are not a histological entity, as the microanatomic features did not distinguish them from their surrounding skin, but rather a configurational change due to mechanical stresses on the skin. He noted that these changes occurred more prominently in actically damaged regions due to deterioration of the elastic fibers. Kligman proposed that the facial frown lines occurred primarily through muscular contraction and that the facial muscles are inserted into the overlying skin. Their muscular contraction throws the skin into...
Botulinum Toxins

Folds because while the muscles can contract, the skin does not. He stated that in youth, dynamic expression lines disappear immediately when the muscles relax since elastic fibers are not yet altered; however, muscular contractions on a degraded dermal matrix result in permanent wrinkles [1].

Bosset et al. analyzed the histological features of the pre-auricular wrinkle compared to retroauricular skin in 16 subjects undergoing face lifts (ages 36–94 years). In doing so, they defined four types of facial skin depressions and classified them based on their depths: (i) invaginations of the skin structures from 250 to 400 μm deep were folds such as nasolabial and melolabial, (ii) permanent wrinkles are invaginations of the skin structures of 100 μm deep, (iii) reducible wrinkles (frown lines, crow lines and preauricular wrinkles) are seen in vivo but not after histologic processing, and (iv) microrelief (nonspecific frown lines due to aging) are shallow depressions (10–30 μm deep) involving the horny and granular layers of the epidermis [2].

Histological analysis of the epidermis and dermis of the skin specifically under and surrounding permanent and reducible wrinkles actually demonstrated normal skin morphology; however, deep permanent wrinkles showed a heavier accumulation of basophilic fibers representing actinic elastosis – which involves the entire depth of the superficial dermis in contrast to reducible wrinkles. This suggests that the development of wrinkles could be furthered by actinic elastosis and the disappearance of microfibrils and collagen fibers at the dermal–epidermal junction (DEJ). The authors concluded that a diminished skin resistance at the DEJ and upper superficial dermis due to sun damage is a prerequisite for wrinkle formation.

However, Pierard and Lapiere [3] concluded that the histological changes necessary to produce a wrinkle began with the changes in the hypodermal connective tissue septae below the wrinkles and not actually in the epidermis or dermis. Underneath each wrinkle there were hypodermal septae that were shorter and thicker than those outside the grooves. They postulated that wrinkling was the result of skin remodeling of the hypodermal connective tissue by repetitive mechanical stimuli induced by striated muscle [3].

Facial Fat Compartments

Neuromodulators are frequently injected with filling agents as part of a comprehensive facial rejuvenation plan. Knowledge of facial fat compartments is paramount for expert injectors to properly restore volume with filling agents. Knowledge of cutaneous anatomy in general is necessary to visualize areas in patients that need to be relaxed (neuromodulators), volume restored (fillers), and resurfaced (lasers/chemical peels). This should be the goal of every injector to create a natural, youthful, and rested appearance. Understanding the following key principles regarding fat compartments will help to further that goal (Figure 2.1).

Forehead and Temporal Fat Compartments

Subcutaneous forehead fat is composed of three anatomical units – central, middle and lateral temporal/cheek fat.

Figure 2.1 Facial fat compartments. Source: Rohrich 2007 [14]. Reproduced with permission of Wolters Kluwer Health, Inc.
The central fat is in the midline region of the forehead and is bounded inferiorly at the nasal dorsum and is bounded laterally by a dense fascial plane that appears to be the central temporal septum. This dense fibrous band septum underlies the fascia of the frontalis muscle and inserts into the dermis.

The middle forehead fat sits on either side of the midline central fat, and is medial to the superior temporal septum. The middle forehead fat compartment is bound inferiorly by the orbicularis oculi retaining ligament of the superior orbit.

The lateral temporal/cheek compartment connects the lateral forehead fat to the lateral cheek and cervical fat. The lateral temporal cheek septum spans the forehead with the neck [14].

The Orbital Fat Compartment

There are also three periorbital fat compartments—superior orbital fat, inferior orbital fat, and lateral orbital fat. Loss of periorbital fat contributes to the appearance of rhytids and lax skin, which are treated with combinations of toxins, fillers, and resurfacing.

The superior orbital fat is bounded by the orbicularis oculi retaining ligament of the superior orbit. The orbicularis retaining ligament is circumferential and spans the superior and inferior orbits blending into the medial and lateral canthi; however, the superior and inferior compartments are distinct from each other.

The inferior orbital fat is a thin layer that lies directly below the inferior lid tarsus. It is bounded inferiorly by the orbicularis oculi retaining ligament or malar septum, and medially and laterally by the respective canthi.

The lateral orbital fat is bounded superiorly by the inferior temporal septum and inferiorly by the superior cheek septum. The zygomaticus major muscle adheres to this compartment. To elevate medial cheek fat or jowl fat, one has to traverse the zygomaticus muscle. There is the potential, while chasing inferior crow’s feet wrinkles with botulinum toxin, of inadvertently injecting the superior aspect of the zygomaticus muscle, which would then result in depression of the cheek and oral commissure.

The Nasolabial Fat Compartment

Prominence of the nasolabial fold is seen in patients with more severe facial volume loss. The nasolabial fold is one discrete unit with distinct anatomical boundaries. The nasolabial fat compartment lies immediately anterior to the medial compartment of malar cheek fat and overlaps jowl fat. It is bounded superiorly by the orbicularis oculi retaining ligament of the inferior orbit and by the sub-orbicularis fat laterally. The inferior border of the zygomaticus major muscle is tethered to the nasolabial fat compartment. The medial cheek septum separates the nasolabial fat from the medial cheek fat.

The Cheek Fat Compartment

The Malar fat compartment is divided into three units—medial, middle, and lateral temporal cheek fat.

The medial cheek fat is lateral to the nasolabial fold. It is bounded superiorly by the orbicularis oculi retaining ligament of the inferior orbit, laterally by the middle cheek septum and inferiorly by jowl fat. The medial cheek septum then separates the nasolabial fat from the medial cheek fat.

The middle cheek fat lies between the medial and lateral temporal-cheek compartments and is anterior and superficial to the parotid gland. The zygomaticus major muscle adheres to its superior portion. The medial and middle cheek fat compartments abut each other but are clearly separated by the middle cheek septum. Their septal boundaries fuse forming a dense fascial network known as the zygomatic ligament.

The most lateral component of the cheek fat is the lateral temporal-cheek compartment. The lateral temporal cheek fat is directly superficial to the parotid gland connecting the temporal fat to the cervical
subcutaneous fat. Anterior to this compartment, the lateral cheek septum appears as a vertical septal barrier. It is the first zone encountered surgically during a face lift procedure after a preauricular incision moving medially.

**The Jowl Fat Compartment**

Jowl fat is the most inferior facial fat. Nasolabial fat and medial cheek fat are located superiorly to jowl fat. Its medial boundary is the depressor anguli oris (DAO) muscle (lip depressor) while the inferior boundary is the membranous fusion of the platysma. The fusion point of the DAO and the platysma is the mandibular retaining ligament. It is not known how this particular compartment behaves during the aging process, but it is probably the most important with regards to midfacial aging.

**Superficial Musculoaponeurotic System**

The superficial musculoaponeurotic system (SMAS) is a complex fibromuscular network which serves a distinct role in the face. Superiorly, it is comprised of the galea aponeurotica in the region of the forehead. Here it divides and envelops the frontalis muscle. Laterally, the fascia becomes the temporoparietal fascia as it approaches the zygomatic arch. It is here in the temporoparietal fascia where the temporal branch of the facial nerve resides. This branch is in close relationship to the periosteum of the zygomatic arch. In the cheek, there is a distinct SMAS layer which becomes contiguous with the platysma in the neck. Embryologically the SMAS develops from an upper division comprising the frontalis, orbicularis oculi, lip elevators, and the orbicularis oris. There is also a lower division made up of the actual platysma muscle along with the depressor anguli oris and risorius [16].

The SMAS separates the subcutaneous fat into superficial and deep layers. The superficial layer, as mentioned, is divided into fat compartments. In between these compartments are complex fascial condensations forming a network of retaining ligaments. It is this network that helps to transmit the forces of the fascial musculature to the skin surface – allowing for a myriad of complex facial expressions which characterize the human face as well as being responsible for the formation of hyperfunctional rhytids.

**The Facial Nerve**

Found below the SMAS in the deep fat layer is the facial nerve. It is this nerve that innervates the distribution of the hyoid arch mesenchyme (second branchial arch) – which is the embryologic precursor of the facial musculature. The facial nerve (seventh cranial nerve) arises from the stylomastoid foramen of the base of the skull. As it exits the foramen it immediately gives off a posterior auricular branch, which supplies the occipitalis, posterior and superior auricular muscles. It also gives off a branch to the posterior belly of the digastric muscle and the stylohyoid muscle. Next, as the nerve passes as a main trunk anteriorly, it then divides into two main divisions in the body of the parotid gland. The upper division is comprised of the temporofacial segment, and the lower division is comprised of the cervicofacial segment. However, as these divisions proceed more anteriorly, extensive variability of branching patterns may develop with variable patterns of innervation ensuing. The temporal branch runs in the temporoparietal fascia after crossing over the zygomatic arch. It becomes the frontal branch as it enters the lateral and deep aspect of the frontalis muscle. The temporal branch supplies the anterior and superior auricular muscles and the superior portion of the orbicularis oculi as well as the corrugators. The corrugator muscles are also supplied by a branch of the zygomatic nerve.

The zygomatic nerve supplies the lower portion of the orbicularis oculi, the corrugators, the muscles of the nasal aperture
including the nasalis and the upper lip elevators. The buccal branch innervates the upper lip sphincteric mechanism with contributions also innervating the upper lip elevators. The marginal mandibular nerve innervates the musculature of the lower lip: the orbicularis oris, the lower lip depressors, depressor anguli oris (DAO), depressor labii inferioris (DLI) and mentalis. The cervical branch innervates the platysma. There is extensive and significant anastomosis between the buccal and zygomatic branches. However, the temporal and marginal branches lack such anastomotic connections. As such, injury to the temporal or marginal nerves during surgery may result in longer lasting paresis. Neurotoxin may be injected into the contralateral musculature to maintain symmetry until the paresis resolves which may or may not occur. For example, if a temporal nerve is unilaterally compromised limiting ipsilateral brow elevation, restoration of symmetry can occur if the neurotoxin is injected into the contralateral frontalis muscle until the temporal nerve function returns on the affected side. The same principle applies to injury of the marginal mandibular nerve and treating the contralateral DAO and DLI muscles to create a more symmetric smile until nerve function returns. If the nerve has been injured and not transected, function usually returns within 6 months to 1 year.

**Vasculature of the Face**

The vasculature of the face is essentially comprised of branches from the internal and external carotid arteries. Examples include the supratrochlear, supraorbital, infraorbital and mental arteries – which accompany their corresponding nerves and exit the corresponding foramina of the central face.

The external carotid artery feeds primarily the maxilla, mandible, occipital and temporal regions of the face. The main branches of the external carotid artery include the facial, internal maxillary, occipital, superficial temporal, posterior auricular and transverse facial arteries. The internal maxillary artery branches into the infraorbital, the inferior alveolar, which eventually becomes the mental artery, and the posterior superior alveolar arteries. The facial artery branches into the superior and inferior labial arteries and eventually becomes the angular artery as it approaches the lateral aspect of the nose.

The internal carotid artery gives off the ophthalmic artery, which then supplies the supratrochlear and supraorbital vessels. Attention should be given to the watershed area that exists between the supratrocholear arteries in the glabellar region. This area of the glabella is prone to necrosis if injecting large volumes of fillers that, in turn, generates external tamponade of the microvasculature in this watershed region. Direct cannulization of vessels has also occurred with fillers in this area, resulting in complete intravascular occlusion [17].

The venous structures of the face tend to follow the arterial pattern, although the venous pattern may have more variability and less predictability. The venous plexus of the lateral orbital and anterior temporal regions drain into the sentinel veins. Care must be taken when injecting neuromodulator agents in the lateral orbital area for crow’s feet treatments to avoid bruising in this region. Magnification and enhanced lighting to identify these vessels as best as possible, as well as injecting tangentially and superficially creating dermal wheals, is the optimal way of injecting this region with botulinum toxin to try to avoid bruising.

**Muscles of Facial Expression**

To have a successful understanding of the injection technique of neurotoxins for facial reshaping and rhytids, it is imperative to have a working understanding of the muscles of facial expression. Thorough knowledge of muscular anatomy also minimizes complications and allows us to precisely tailor injections to the patient’s aesthetic desires. Knowing the origin, insertion, caliber or size,
course, functional and aesthetic action of each muscle is paramount to successfully treating the facial muscles with neurotoxins. Most facial muscles originate on the facial skeleton and insert on the dermis of the skin with assistance from the superficial musculoaponeurotic system – thus transmitting their forces to the overlying skin and significant facial structures, such as the brows and oral commissures.

The following is an in-depth look at the anatomy of the facial musculature with clinical correlation. The face will be divided into upper, middle, and lower thirds. The neck primarily has the platysma muscle as its major contributor of facial expression and will be discussed last. Although the discussion involves individual analyses, it is important to remember that an intricate interplay exists between the muscles of facial expression. Each facial expression involves multiple muscles, creating antagonist/protagonist activity to result in a unique expression (Figure 2.2).

The Upper Face

Before discussing the specific muscles of the upper one-third of the face, it is critical to understand the ideal aesthetic position of the overlying skin and soft tissue, particularly the brow. Much media attention has focused on incorrect brow placement after botulinum toxin injection over the past several years. The terms “Nicholson brow,” “Spock brow” or “mephisto-look” are now part of the vernacular of those familiar with cosmetic toxin injection, and the astute clinician understands...
the importance of minimizing this type of appearance.

There are more similarities than differences between the male and female brow (Figure 2.3). The edge of the eyebrow lies in a vertical plane passing through the alar base. The lateral eyebrow ends at an oblique line drawn from the alar base through the lateral canthus. The medial and lateral ends of the eyebrow lie at the same horizontal level in both males and females. The apex of the eyebrow lies vertically above the supraorbital rim in women and lies at the rim in men and the male eyebrow tends to be heavier and less arched.

The muscles of the upper one-third of the face are critical with respect to the shape and position of the brows and the presence of hyperfunctional rhytids (Table 2.1). These rhytids include the transverse rhytids of the forehead, the vertical and horizontal glabellar frown lines, as well as lateral canthal crow’s-feet. The shape and size of the palpebral aperture is intimately associated with function of the orbicularis oculi muscle. The shape and position of the brow exemplifies the antagonist and protagonist relationship that occurs in the musculature of the upper one-third of the face. The frontalis muscle is a paired muscle that forms the anterior part of the occipitofrontalis (epicranius) muscle. It is connected to the posterior occipitalis muscle via the galea aponeurotica, and therefore does not have a bony origin as most facial muscles do. It inserts into the skin of the lower forehead in the region of the brows and interdigitates with the corrugator, procerus and orbicularis oculi muscles. It is this interdigititation with these muscles that allows it to have a unique role in determining not only the position of the brow but also the shape of the brow. The frontalis muscle is the only elevator of the brow complex, and therefore should be treated conservatively when using neurotoxins. Avoiding injection of neurotoxin to the lower one-third of the frontalis in general is helpful in many patients to preventing brow ptosis and maintaining some brow movement. The frontalis muscle is also responsible for the creation of the transverse rhytids of the forehead. These rhytids may become deeper in time as the frontalis muscle becomes more active to compensate for eyelid ptosis. This hyperfunctional compensatory mechanism is seen in older patients as they try to compensate for ptosis that is occurring from the dis-insertion of the levator aponeurosis from the superior aspect of

Figure 2.3 Female and male brow position. Redrawn based on an original drawing by David M. Ozog.
Table 2.1  Muscles of the brow complex.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Origin</th>
<th>Insertion</th>
<th>Action</th>
<th>Cosmetic consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyebrow depressors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrugator supercilli</td>
<td>Medial inferior aspect of frontal bone near nasofrontal suture and medial superior orbital rim</td>
<td>Skin above medial brow</td>
<td>Adducts and depresses medial brow</td>
<td>Vertical frown lines of glabella</td>
</tr>
<tr>
<td>Procerus</td>
<td>Inferior aspect of nasal bones and upper lateral nasal cartilages</td>
<td>Dermis of glabella and lower mid forehead</td>
<td>Downward pull on skin of medial forehead</td>
<td>Transverse rhytids between brows</td>
</tr>
<tr>
<td>Orbicularis oculi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Orbital portion</td>
<td>Medial palpebral ligament, nasal portion of frontal bone and frontal process of maxilla</td>
<td>Cheeks, forehead and temples; interdigitates with surrounding muscles (frontalis and corrugator supercilli)</td>
<td>Depresses medial and lateral aspers of brow; adducts brow</td>
<td>Lateral canthal rhytids (crow’s feet)</td>
</tr>
<tr>
<td>Eyebrow elevators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontalis</td>
<td>Galea aponeurotica</td>
<td>Skin of lower forehead; interdigitates with corrugator, procerus and orbicularis oculi</td>
<td>Elevates brows</td>
<td>Transverse rhytids of forehead</td>
</tr>
</tbody>
</table>

The tarsal plate. Although the frontalis has been classically described as a paired muscle complex, it frequently is contiguous across the forehead, thus explaining the continuous rhytids that are seen in many patients (Figure 2.4). When there is a dehiscence of the muscle, a double arched transverse rhytid pattern may be seen in those patients when raising their eyebrows.

The lateral extent of the frontalis muscle is seen at the temporal fusion line – which is also the medial extent of the temporalis muscle. This is usually the region where the anterior hairline exists. This relationship is important to identify because it explains why lateral brow ptosis occurs with aging. This will be discussed further in detail later.

The corrugator supercilli muscle originates on the medial inferior aspect of the frontal bone near the nasofrontal suture as well as the medial superior orbital rim. It runs laterally and superiorly to insert onto the skin above the medial brow. Its insertion can be seen as a dimple in the skin above the medial brow as the patient frowns (Figure 2.5). This may be seen medial, at or lateral to the mid-pupillary line – depending on the length of the muscle. There may, in fact, be multiple insertions in this region. This corruguator supercilli muscle runs deep to the procerus, frontalis, and