Kyle K. Seo

Botulinum Toxin for Asians

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Kyle K. Seo
Modelo Clinic
Seoul
Korea

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To my mother, In-Soon Kim, and my late father, Jae-Kwan Seo, who passed away 8 years ago and is dearly missed. Their love, encouragement, and inspiration challenged me to dream bigger and to reach higher.

Foreword

We first had the pleasure of meeting Dr. Kyle Seo in 2000 when we visited Seoul. We were immediately impressed with his high level of understanding of botulinum toxin therapy as well as other therapeutic modalities in the cosmetic arena. Since that time, our admiration of him and our appreciation of his knowledge and innovation have rapidly grown. Dr. Seo is truly one of the great international experts in this field. We always pay attention when he presents or writes.

The areas where he has extensive knowledge and experience include the botulinum toxins and other noninvasive cosmetic treatment modalities. He is especially expert in the differences between Korean and Asian patients' ideals of beauty and those of Caucasian patients. He has published extensively on these and has helped us all to better understand these differences. This book is titled *Botulinum Toxin for Asians* and in the preface Dr. Seo writes "In this regard the book is aimed at providing practical guidance not only for Asian doctors but also for Western doctors in treating patients of Asian ethnicity." This would lead one to believe that this describes the main virtue of this book, and in our estimation, this book has much wider appeal than that. Dr. Seo has extensive knowledge and experience of the underlying biochemistry and physiology and anatomy which is beautifully summarized in this book. The illustrations are world class. We believe that this volume is essential reading for all individuals concerned with the cosmetic treatment of men and women throughout the world be they Asians and non-Asians!!

This book is an elegant distillation of Dr. Seo's knowledge and experience in this area, and as such he has advanced the clinical use of botulinum toxin to improve both facial and nonfacial problems. It is essential reading for all of us who use botulinum toxin cosmetically and those who are interested in this indication.

We salute Dr. Seo for all that he has done for us over the past years!

Alastair Carruthers
Jean Carruthers

Preface

Botulinum toxin treatment serves as a doorway for patients who are entering the world of cosmetic procedures for the very first time. Any vague concern or fear they might have had of cosmetic treatments in general is quickly dispelled with this simple 5-min procedure, leaving them amazed and thrilled at how effortless it can be to restore their youth and beauty. Happy patients in turn become loyal patients who are more apt to take the next big step into trying other more invasive cosmetic procedures. From a financial point of view, therefore, botulinum toxin treatments can become a significant contributor to the clinic's overall bottom line. Conversely, however, patients who experience negative results from their initial botulinum toxin treatment may never visit the clinic again. This underlines the significance of botulinum toxin treatments as the essential starting point and stepping stone for doctors in laying the foundation for mutual trust and relationship with their patients.

One common misconception regarding botulinum toxin treatments, perhaps relating to the simplicity of the procedure which involves only a few injections, is that the outcomes obtained would be more or less consistent regardless of the skill or experience of the individual practitioner. However, in my practice, I have seen many of my former patients return only after suffering from adverse effects from botulinum toxin procedures they received from other clinics. In case of a botulinum toxin procedure gone awry, there exists unfortunately little room for medical intervention, and patients are left to bear with their unnatural facial expressions for at least 2 months with no recourse other than waiting for the effects of the toxin to fade away. This is because there are no effective antidotes for botulinum toxin. Indeed, the importance of taking proper precautions in performing botulinum toxin procedures cannot be emphasized enough. Shortly after I began practicing botulinum toxin procedures, I also encountered various adverse effects with my patients, which had caused me great anguish at the time and to this day I am still unable to completely shake off. It is against this backdrop that this book was written, with the hope of providing fellow practitioners who are either just starting out on their career in botulinum toxin treatments or who still lack confidence in performing this procedure with the equivalent of a *Driver's Manual* laying out the safe treatment practices based on the trials and errors which I personally confess to have committed during the early days of my own practice.

Upon reflection, many of my earlier mistakes arose from the failure to fully appreciate the difference in facial shape and beauty standards between

Asians and Caucasians. For example, the Asian face tends to be wider and flatter compared to the more dimensional and relatively narrower Caucasian face. Whereas having a prominent zygoma and square jaws is regarded within Western cultures as an appealing beauty trait, zygoma reduction surgery and square jaw reduction with botulinum toxin are popular among Asians who wish to reduce the size of their wide faces. The higher cases of negative results I had encountered with Asian patients were most probably due to applying the same injection methods suitable for Caucasians to Asians, producing outcomes which deviated from the Asian beauty standard. In these pages, I have attempted, therefore, to provide a comprehensive summary of the various botulinum toxin injection techniques suitable for Asians based on my clinical cases and field experiences. In this regard, the book is aimed at providing practical guidance not only for Asian doctors but also for Western doctors in treating patients of Asian ethnicity. Of course, Asians are not a homogeneous group, and the term "Asian" in this book is used in a narrow sense, referring primarily to people from East Asia such as the Chinese, Japanese, and Koreans, and does not extend to cover those from other parts of Asia such as Arabics or Indians. That said, however, Korean beauty, for what it is worth, is currently the dominant Asian beauty standard, driven by the strong influence of the Korean wave in many parts of the world through K-pop, K-dramas, etc. In fact, it is attracting many foreign patients from China, Japan, and Southeast Asia to visit Korea for cosmetic treatment. In some respects, therefore, this book can offer solutions generally applicable to Asian patients who aspire to attain features of the dominant Asian beauty standard regardless of their individual nationality.

The injection methods prescribed in this book do not reflect the Asian consensus data but instead illustrate the specific techniques I actually employ in my field practice. In fairness, different doctors may have different views and ideas on some of the points I cover. That notwithstanding, the injection methods presented in this book have been established based on thousands of cases performed over the past 18 years and will be of relevance for those seeking helpful practical pointers. To the extent that no single method can be upheld as absolutely perfect, however, I am more than happy to receive wise contrary advice from learned colleagues reading this book.

It is my sincere hope that this English version of *Botulinum Toxin for Asians* will become a valuable and beloved source of new knowledge and advice for interested readers all over the world.

Seoul, Korea Kyle K. Seo
May, 2016

Acknowledgments

Many people assisted in the publication of this book. I am grateful to my staff for compiling the numerous underlying materials and pictures for this book. I am greatly indebted to my friend, anatomist Professor Hee-Jin Kim who provided me with excellent photos and valuable input in the field of anatomy and Mr. Kwan-hyun Yoon, the Mediart representative who helped to greatly improve the quality of this book with his accurate and elaborate anatomic illustrations. Most importantly, I owe a special thanks to my mentor and essayist Professor Hee Chul Eun who prepared the initial draft for the English edition of this book drawing on his extensive medical knowledge and literary sense. Finally, my thanks goes to Mr. Sam Oh and Ms. San-Hyo Kim, English editors whose efforts helped to bridge the language barrier and put together what I hope will be a compelling medical textbook for readers across the world.

Contents

1 Botoxology 1
1.1 Introduction 1
1.2 Terminology Related to Wrinkles 2
1.2.1 Basic Terminology Related to Wrinkles 2
1.2.2 Functional Aspect. 3
1.2.3 Severity Aspect 4
1.3 Basic Science of Botulinum Toxin. 4
1.3.1 Serotypes and Mechanism of Action of Botulinum Toxin 4
1.3.2 Molecular Structure of Botulinum Toxin Type A 4
1.3.3 Sites of Action 5
1.3.4 Recovery 6
1.3.5 Dosage and Potency Assays. 7
1.3.6 Difference in Personal Sensitivity 9
1.3.7 Effects on Sensory Nervous System 11
1.4 Comparison of Products. 12
1.4.1 Comparison of Potency 12
1.4.2 Comparison of Excipients 14
1.4.3 BOTOX®: “Golden Standard” 14
1.4.4 Dysport®: “European Standard”. 14
1.4.5 Neuronox® : “The First Korean Botulinum Toxin” . . . 15
1.4.6 Myobloc®: “Unique Type B Botulinum Toxin”. 15
1.4.7 Xeomin®: “Second-Generation Botulinum Toxin” . . . 16
1.4.8 BTXA® : “China Toxin”. 17
1.4.9 Botulax®. 18
1.4.10 Nabota® 18
1.4.11 Innotox® “Botulinum Toxin Endorsed by BOTOX®” . 18
1.5 Immunogenicity/Immunoresistance. 19
1.6 Safety 20
1.6.1 Human Lethal Dose 20
1.6.2 Overdose 21
1.6.3 Botulinum Toxin and Children 21
1.6.4 Botulinum Toxin and Pregnancy 21
1.6.5 Botulinum Toxin and Hypersensitivity 22

1.7 Reconstitution, Dilution, and Storage of Botulinum Toxin 22
1.7.1 Reconstitution and Dilution 22
1.7.2 Storage 23
1.8 Contraindications 26
1.8.1 Absolute Contraindicaitons 26
1.8.2 Individuals Injected with Caution 26
1.9 Characteristics of the Procedure (EAT Classification) 26
References 27

2 Wrinkle Treatment with Botulinum Toxin 29
2.1 Introduction 29
2.1.1 Effective and Noneffective Wrinkles in Botulinum Toxin Treatment 30
2.1.2 Communication 32
2.1.3 Pretreatment Assessment 35
2.1.4 Ethnic Differences Between Asians and Caucasians . . 37
2.1.5 Appropriate Interval for Touch-Up Injection and Repeat Injection 43
2.1.6 Preventative Effect of Botulinum Toxin for the Treatment of Wrinkles 44
2.1.7 Botulinum Rebalancing (Compensatory Hyperactivity) 44
2.1.8 Botulinum Remodeling of Facial Expression 47
2.1.9 Injection Techniques 48
2.1.10 Adverse Effects 49
2.2 Regional Particulars 54
2.2.1 Lateral Canthal Rhytides 54
2.2.2 Eyelid Ptosis 60
2.2.3 Upper Palpebral Lines 62
2.2.4 Infraorbital Wrinkles 62
2.2.5 Horizontal Forehead Lines 65
2.2.6 Eyebrow Shaping/Eyebrow Lifting 71
2.2.7 Glabellar Frown Lines 72
2.2.8 Bunny Lines/Nasal Side Wall Scrunch Wrinkles 82
2.2.9 Horizontal Radix Lines 83
2.2.10 Nasal Tip Elevation 85
2.2.11 Excessive Gingival Display/Gummy Smile 86
2.2.12 Nasolabial Folds, Asymmetric Smile 87
2.2.13 Ala Band and Dimpling 91
2.2.14 Perioral Lines (Purse-String Lips) 92
2.2.15 Mouth Corner Elevation 93
2.2.16 Mentalis Hyperactivity/Cobblestone Chin 97
2.2.17 Platysma Band 99
References 103

3 Facial Contouring with Botulinum Toxin 107
3.1 Square Jaw/Masseter Hypertrophy 107
3.1.1 Mechanism of Action: Disuse Atrophy 109
3.1.2 Causes of Masseter Muscle Hypertrophy 109
3.1.3 Pretreatment Assessment 110
3.1.4 Self-Assessment 111
3.1.5 Anatomy 111
3.1.6 Injection Techniques 112
3.1.7 Injection Dose 113
3.1.8 Change of Masseter Volume 117
3.1.9 Onset and Duration of Effect 117
3.1.10 Appropriate Interval and Dose for Repeat Injections 121
3.1.11 Adverse Effects 121
3.1.12 Effect of Botulinum Toxin Injection on the Mandibular Bone 126
3.2 Temporalis Hypertrophy 127
3.2.1 Anatomy 127
3.2.2 Injection Techniques 127
3.2.3 Adverse Effects 127
3.3 Salivary Gland Enlargement 129
3.3.1 Parotid Gland Enlargement 129
3.3.2 Submandibular Gland Enlargement 131
3.3.3 Injection Techniques 131
References 133

4 Multiple Intradermal Botulinum Toxin Injections 135
4.1 Concept 135
4.2 Injection Techniques 138
References 139

5 Body Contouring with Botulinum Toxin 141
5.1 Introduction 141
5.1.1 Reconstitution of Botulinum Toxin 141
5.1.2 Dose 141
5.1.3 Injection Techniques 141
5.1.4 Appropriate Time and Dose for Repeated Injection 142
5.1.5 Adverse Effects 142
5.2 Regional Particulars 142
5.2.1 Shoulder Contouring (Trapezius Muscle) 142
5.2.2 Arm Contouring (Deltoid Muscle) 143
5.2.3 Thigh Contouring (Quadriceps Femoris Muscle) 147
5.2.4 Calf Contouring (Gastrocnemius Muscle) 148
References 157

6 Hyperhidrosis Treatment with Botulinum Toxin 159
6.1 Introduction 159
6.1.1 Etiology and Classification of Hyperhidrosis 159
6.1.2 Epidemiology of Focal Hyperhidrosis 159
6.1.3 Diagnosis of Focal Hyperhidrosis 160
6.1.4 Effects of Focal Hyperhidrosis on the Patients' Daily Lives 160
6.1.5 Treatment of Focal Hyperhidrosis 160
6.1.6 Treatment of Focal Hyperhidrosis with Botulinum Toxin 162
6.2 Regional Particulars 166
6.2.1 Axillary Hyperhidrosis 166
6.2.2 Palmar Hyperhidrosis 167
6.2.3 Plantar Hyperhidrosis 172
6.2.4 Facial Hyperhidrosis and Scalp Hyperhidrosis 174
6.2.5 Gustatory Hyperhidrosis 177
6.2.6 Compensatory Hyperhidrosis 178
6.2.7 Bromhidrosis/Osmidrosis 178
6.2.8 Other Diseases Responsive to Botulinum Toxin 179
6.2.9 Effects of Botulinum Toxin Type B on Focal Hyperhidrosis 179
References 181

About the Author

Kyle Koo-Il Seo is a dermatologist based in Seoul. He received his M.D. and Ph.D. from Seoul National University's College of Medicine, Seoul, South Korea. He became a Clinical Associate Professor in the Department of Dermatology of Seoul National University College of Medicine as the chief of the Botox Clinic. Presently he is also the Director of Modelo Clinic in Seoul, South Korea.

Dr. Seo has worldwide reputation as an authority in the field of botulinum toxin and fillers. He was the first doctor in Korea to have launched a hands-on training course on botulinum toxin and fillers, namely, the 'Modelo Academy', open since 2002. He has also published extensively on the areas of botulinum toxin and filler treatments including Botulinum Toxin for Asians (in Korean) (Seoul Medical Publishing Ltd, 2014) and *Clinical Anatomy of Face for Botulinum Toxin and Filler Injection* (Springer, 2016). In recognition of his exceptional dedication and prominent academic achievements, Dr. Seo was ultimately selected as the sole keynote speaker to represent the entire global cosmetic field at the plenary session of the 23rd World Congress of Dermatology (Vancouver 2015).

Dr. Seo also dedicated himself to promoting global academic activity in the dermatology society as the Vice President of the local organizing committee for the 22nd World Congress of Dermatology (WCD) (Seoul, 2011) and the Secretary General of the local organizing committee for the 36th annual meeting of the International Society for Dermatologic Surgery (ISDS).

Botoxology

1

1.1 Introduction

Botulinum toxin type A (BoNT-A) is a neurotoxin produced by the gram-negative, rod-shaped bacterium *Clostridium botulinum*. It causes muscle paralysis through inhibition of acetylcholine release at the neuromuscular junction. Since the ingenious American ophthalmologist Dr. Alan Scott first used the BoNT-A to treat patients with strabismus, BoNT-A exploded in popularity and has since been used in treating a number of inappropriate excessive muscle contractions including blepharospasm and cervical dystonia. In the late 1980s, during a clinical study for treating blepharospasm with BoNT-A, a Canadian ophthalmologist, Jean Carruthers, observed that patients participating in the study wanted to continue to receive BoNT-A injection despite of improvement of blepharospasm because glabellar lines and periorbital lines disappeared along with blepharospasm. She mentioned this interesting observation to her husband, Alastair Carruthers, a dermatologist. This led to publish the world's first article using BoNT-A for wrinkle treatment [1]. Since then BoNT-A has become a byword for the treatment of wrinkles.

Since approved to treat blepharospasm and strabismus by the US FDA in 1989, BoNT-A has continued to expand its indication for the treatment of inappropriate excessive muscle contractions including cervical dystonia (approved by the US FDA in 2000), focal upper limb spasticity (approved by the US FDA in 2010), detrusor overactivity (neurogenic bladder) (approved by the US FDA in 2011), juvenile cerebral palsy, stroke (for rehabilitation therapy), and anal fissure. The BoNT-A has also been proven highly effective in treating focal hyperhidrosis of the axillae (approved by the US FDA in 2004), palms, and soles, since it inhibits secretion of the eccrine sweat glands innervated by the sympathetic nervous system. In addition, though exact mechanism is not elucidated in humans yet, it was found in an animal experiment that the BoNT-A inhibited secretion of pain-inducing neurotransmitters such as substance P. Pain relief such as in chronic migraine (approved by the US FDA in 2010) is an another good example of the continually broadening applications of BoNT-A.

The use of BoNT-A for aesthetic purposes is also beyond traditional wrinkle treatment. For example, intradermal BoNT-A, considered as a full package of antiaging effects that BoNT-A can deliver, is not only for the reduction of dynamic facial wrinkles but also for the reduction of static wrinkles and pore sizes, as well as creating the so-called perceived "lifted look". What's more, nonsurgical cosmetic treatments such as facial contouring and body contouring based on the principle of disuse muscle atrophy have recently come in to the limelight.

Indeed, BoNT-A is a so fantastic drug continuously expanding its applications in various fields such that the term "botoxology" may be used for this new field of study. However, this new realm of

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study requires more organized and evidence-based knowledge. In this chapter, basic science and some important knowledge for BoNT-A will be covered in order to deal with particular indications.

1.2 Terminology Related to Wrinkles

Translating this text into English proved difficult from the beginning especially choosing terminology related to wrinkles. I found the terms used to describe wrinkles are not well defined. Several words, such as wrinkle, rhytid, line, crease, groove, and fold, share similar definitions and may be used interchangeably from source to source. Facial expression wrinkles can be classified into dynamic and static wrinkles; however, the word "dynamic" can be sometimes expressed as hyperfunctional or hyperkinetic depending on the authors. The literatures often refer to lines in describing regional wrinkles on specific areas of the face with a combination of other words such as bunny lines. In addition to this, different researchers utilizing different terminology present obvious challenges. I think precise definition and agreement of the terms related to wrinkles are necessary.

Severity is another problem when selecting wrinkle terminology. Adjectives such as deep, severe, and fine can be used to describe wrinkles with a combination. Though image analysis seems to be more thorough than clinical assessments of severity, common terms are necessary for communication between doctors and patients. With consideration to the above, I will define the terms below with precise definitions and additional explanation. These terms will be used throughout the text.

Facial wrinkles and aging signs in Asians are shown in 70-year-old Korean man (Fig. 1.1).

1.2.1 Basic Terminology Related to Wrinkles

Wrinkle This term is the most common word for the general public and covers the most comprehensive concept. Dermatologists use this term when explaining general aspects such as wrinkle treatment, wrinkle severity, and wrinkle prevention.

Rhytid Etymologically, this term is Greek in origin. The rhytid (pluralized as rhytides) has essentially the same meaning of wrinkle [2]. I used the term wrinkle instead of literary expression "rhytid" in this book except lateral canthal rhytides if possible. Except when referencing specific literature from the past, I think this term "rhytid" should be avoided in communication with patients and the general public.

Line Lines are most commonly interchangeable with wrinkles. However, lines usually mean a mild form of wrinkles in severity or wrinkles which are not caused by aging process such as horizontal necklines and bunny lines. Lines sometimes describe the wrinkle in certain locations, such as bunny lines, marionette lines, infraorbital lines, horizontal forehead lines, glabellar frown lines, and preauricular lines.

Crease Crease is also interchangeable with wrinkles and lines. However, a crease is conceptually similar to a mild form of wrinkles in severity. And crease sometimes describes the specific wrinkle in certain locations, such as labiomental crease and proximal wrist crease.

Fold The term fold is quite limited in use but can be used when describing a nasolabial fold, a Mongolian fold (epicanthal fold), and a labiomandibular fold. A fold is conceptually similar to a wrinkle, but with nuances such as linear depression and a mild recurved margin on one side, like pleating. I did not use fold in other situations except to describe the words mentioned above.

Groove The term groove is quite limited in use but can be used when describing a nasojugal groove and a palpebromalar groove. A groove is conceptually similar to a wrinkle, but with nuances such as shallow linear depression, which is slightly wider than a line.

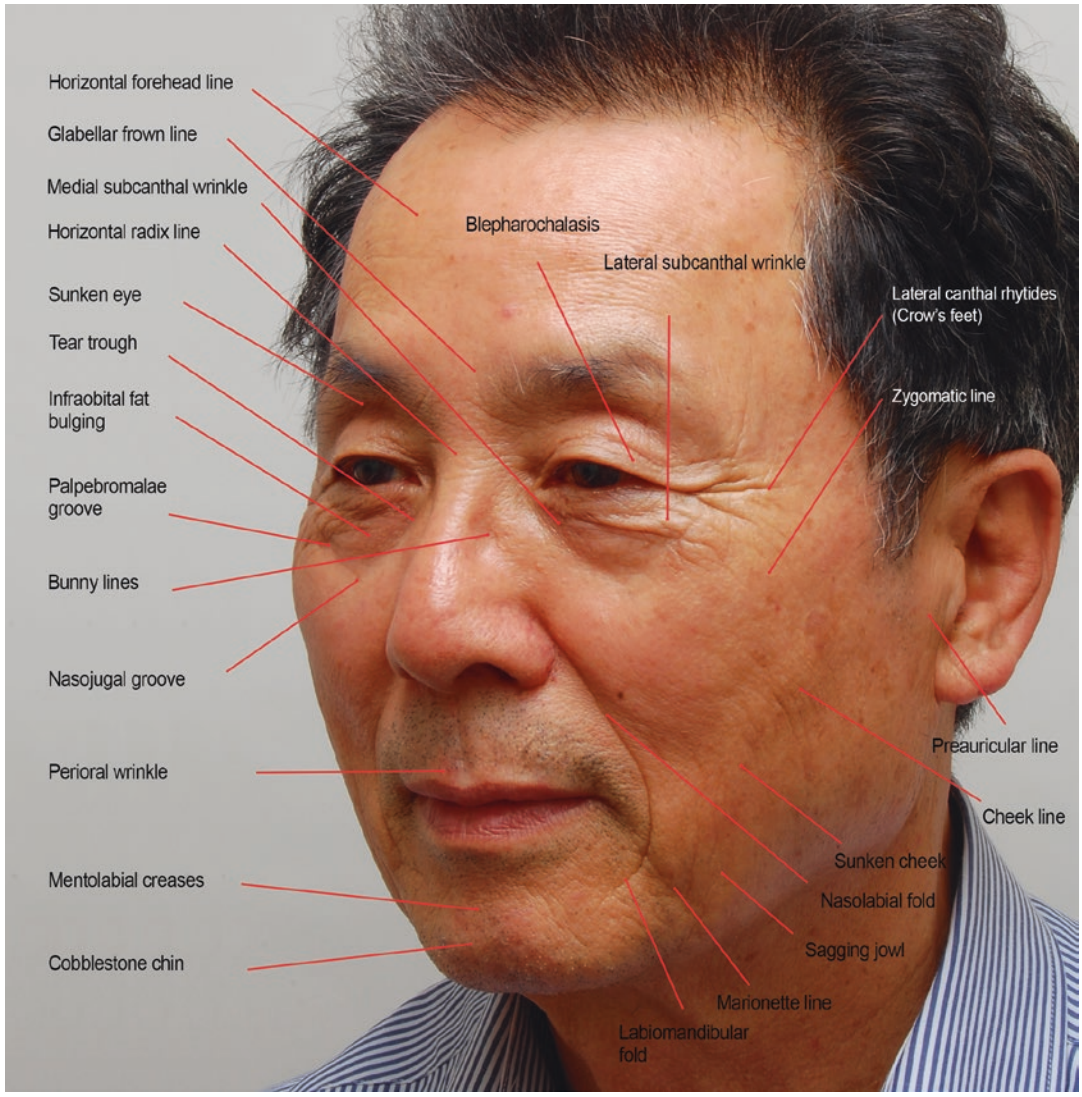

Fig. 1.1 Facial wrinkles in Asians

1.2.2 Functional Aspect

Static Wrinkle Defined as wrinkles unaffected by facial expressions. Commonly referred to as "wrinkles at rest," I believe the term static wrinkle is clearer and more illustrative.

Dynamic Wrinkle The opposite of a static wrinkle, dynamic wrinkles are reversible wrinkles caused by contractions of facial expression muscles. Commonly referred to as "wrinkles at animation," I believe the term dynamic wrinkle is clearer and more illustrative.

Hyperfunctional/Hyperkinetic Wrinkles I have omitted these two terms because the words are a little difficult for general public to understand that they mean wrinkles of facial expressions.

1.2.3 Severity Aspect

Wrinkles can be divided into grades based on severity. I used the terminologies fine line, line (fine wrinkle), moderate wrinkle, and deep wrinkle, defined as follows:

Grade 1 Fine line: wrinkle with barely visible linear depression
Grade 2 Fine wrinkle (line): wrinkle with mild linear depression
Line: used as a synonym of fine wrinkle.
Grade 3 Moderate wrinkle: wrinkle between fine and deep wrinkle
Grade 4 Deep wrinkle: static wrinkle associated with deep furrow

1.3 Basic Science of Botulinum Toxin

1.3.1 Serotypes and Mechanism of Action of Botulinum Toxin

There are seven serotypes of botulinum toxin(BoNT): A, B, C1, D, E, F, and G based on their immunologic properties. Among them, serotypes A, B, and F are well-known neurotoxins. The duration of efficacy and potency differs between serotypes; type A is the most potent and has the longest duration of efficacy. As the muscle paralytic effect of type B is far weaker than type A in humans, a 100-times higher dose is necessary to achieve the same effectiveness. The duration of efficacy of type B is also shorter, allowing muscle function to recover nearly by half after 4 weeks. Type F is potency.

BoNT blocks the release of acetylcholine, a neurotransmitter, by binding to the presynaptic cholinergic nerve terminals in neuromuscular junctions (Fig. 1.2). For synapses, "acetylcholine vesicles" containing acetylcholine should be fused with the plasma membrane of the nerve branch for the release of acetylcholine into neuromuscular synapses. BoNT cleaves the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, a plasma membrane receptor essential for this process. Specific serotypes of the BoNT cleave different plasma membrane receptors; types A and E cleave 25 kDa synaptosomal-associated protein (SNAP-25); types B, D, and F cleave vesicle-associated membrane proteins (VAMP, also known as synaptobrevin), and type C1 cleaves two plasma membrane receptors, syntaxin and SNAP-25 (Fig. 1.3). When injected, BoNT blocks acetylcholine release into the cholinergic synapse, resulting in "chemodenervation."

1.3.2 Molecular Structure of Botulinum Toxin Type A

BoNT-A is a 150 kDa neurotoxin molecule composed of a 100 kDa heavy chain linked via a disulfide bond to a 50 kDa light chain (Fig. 1.4). The heavy chain plays a crucial role in binding the neurotoxin molecule to the axon terminal entering the nerve, while the light chain actually cleaves the plasma membrane receptors (e.g., SNARE complex, SNAP-25) to prevent intracellular fusion of acetylcholine vesicles with the plasma membrane [3]. The neurotoxin molecule of BoNT-A is surrounded and protected by large complexing protein molecules called neurotoxin-associated proteins (NAPs). NAPs are composed of hemagglutinins and a non-toxin non-hemagglutinin (NTNH). Hemagglutinins include four types of proteins, while a single type of NTNH always combines with the neurotoxin. Molecular weights of BoNT-A vary: 300 kDa, 500 kDa, and 900 kDa depending on the size of complexing proteins. Complexing proteins encircle the neurotoxin at acidic pH, while separated from it at a neutral or basic condition. They protect the neurotoxin molecules from the proteases of the gastrointestinal tract (e.g., pancreatic enzymes, pepsin) and gastric acid when ingested by animals. At neutral pH, they are dissociated and the neurotoxin is released. Thus, complexing proteins are the product of evolution, making the bacterial neurotoxin effective to the target animals (how clever it is!) [4]. Their role in the skin and muscles, however, is not well known. On the contrary,

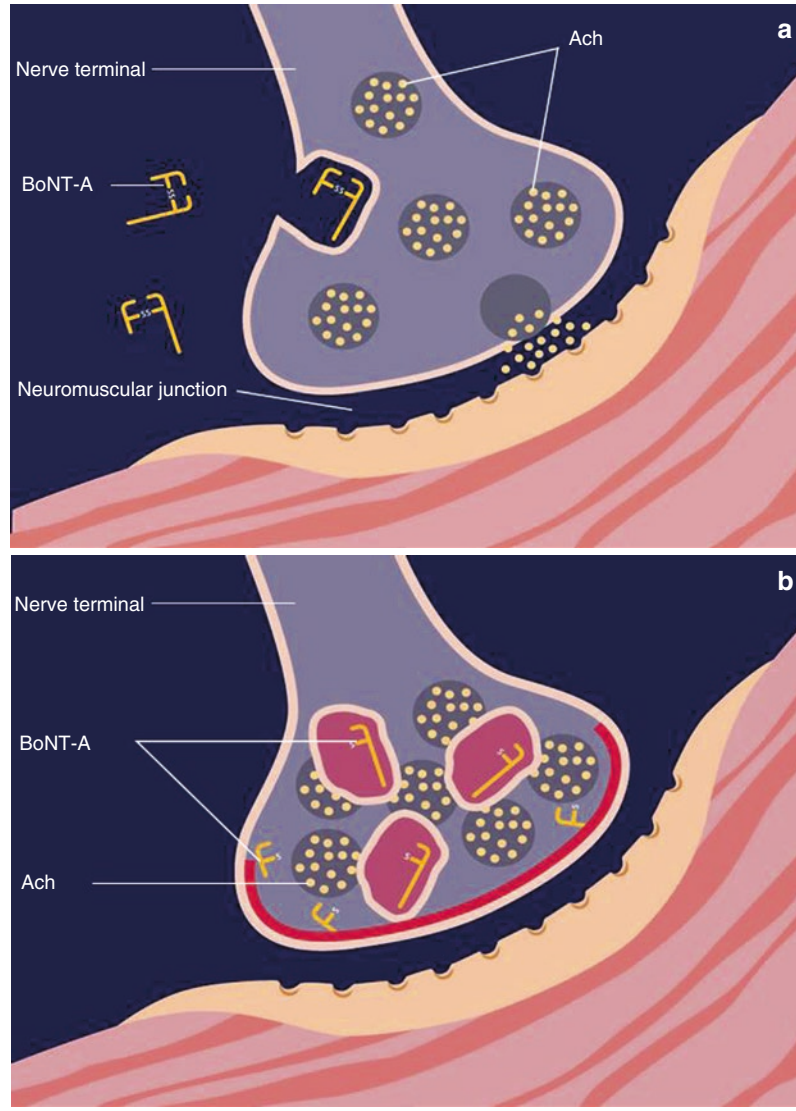

Fig. 1.2 Action mechanism of botulinum toxin (Photo, courtesy of Allergan Korea). (**a**) Normal neuromuscular junction. Acetylcholine (Ach) is released into the neuromuscular junction. (**b**) Neuromuscular junction blocked by botulinum toxin. Acetylcholine release into the neuromuscular junction is blocked

they seem to induce immunologic responses and promote antibody formation.

Allergan has claimed that BOTOX® of high molecular weight (900 kD) is safer than Dysport® of low molecular weight (500–900 kD) because the BoNT-A with larger molecular weight diffuses less to the adjacent muscles. According to Eisele's study, however, once BOTOX® is diluted with normal saline, 85 % of the neurotoxin is present in a free form, and the rest of it is also dissociated to a reduced form of 500 kD molecular weight [5]. Additionally, once injected into the skin of a neutral pH, the complexing protein is released from the core neurotoxin in less than a minute. In summary, the molecular weight of BoNT-A is not an issue of clinical significance.

1.3.3 Sites of Action

The neuromuscular junction is the representative of cholinergic synapses that release acetylcholine. Blockage of acetylcholine release in the neuromuscular junction by BoNT-A leads to muscle paralysis. BoNT-A also inhibits sweat and salivary secretion since the sweat gland and salivary gland

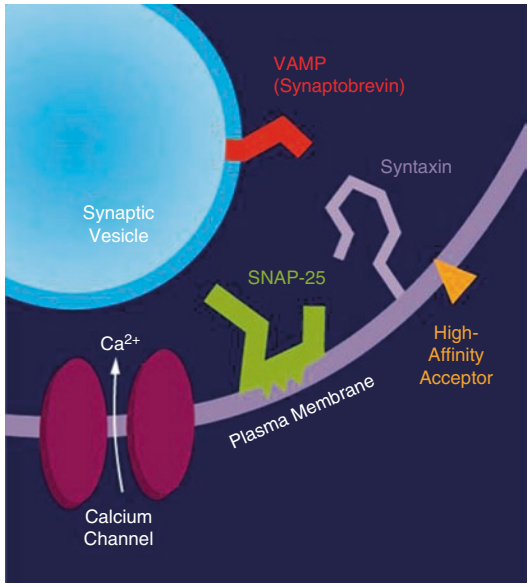

Fig. 1.3 Intracellular target receptors of botulinum toxin (Photo, courtesy of Allergan Korea)

are cholinergic synapses [6, 7]. The sympathetic ganglia may also be suppressed by BoNT-A injection because they are also cholinergic synapses [8].

1.3.4 Recovery

The "chemodenervation" phenomenon by BoNT-A is not permanent but recovers gradually over 1–3 months because of new neuromuscular junction generation (Fig. 1.5). Neuromuscular junctions are in dynamic homeostasis between constant generation and decay; blockage of nerve conduction by BoNT-A induces new axonal sprout, resulting in muscle strength recovery. In humans, the muscle paralytic effect of BoNT-A is known to recover by half after 8 weeks. Therefore, symptoms of blepharospasm may recur when muscle strength recovers only by half, requiring repeat treatment every 2–3 months. Wrinkles, on

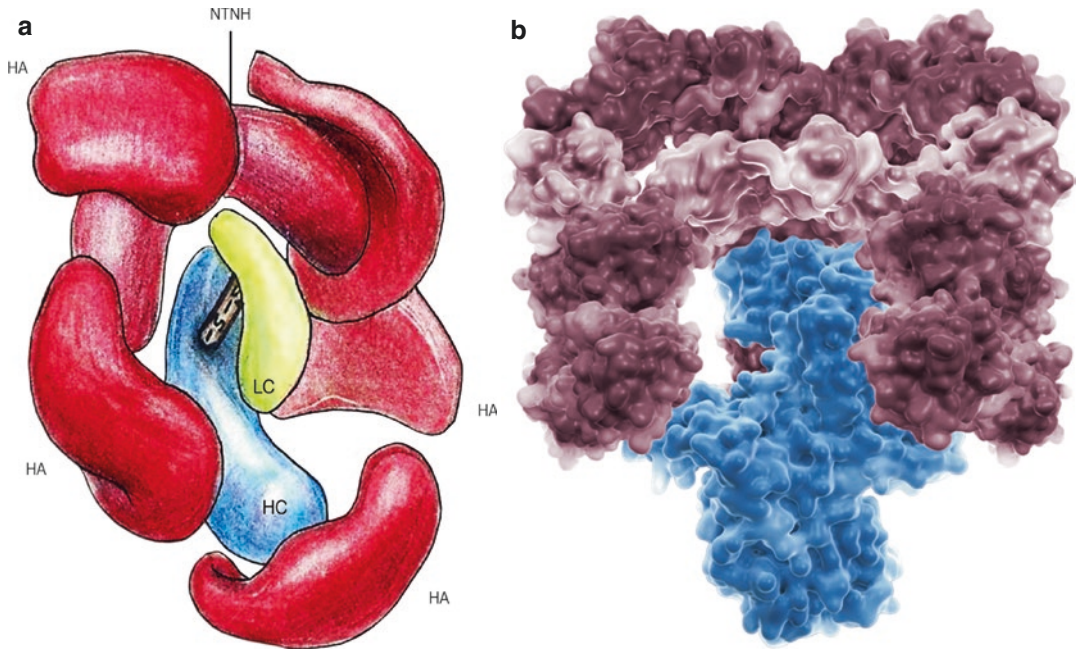

Fig. 1.4 Three-dimensional structure of the botulinum toxin type A protein. (**a**) Structure of botulinum toxin A with 900 kDa molecular weight. The core neurotoxin consisting of light chain and heavy chain is only 150 kDa; the rest is comprised of hemagglutinins (HA) and nontoxic non-hemagglutinin (NTNH) protein that protect the core neurotoxin (illustrated by Jina Seo) (*LC* light chain, *HC* heavy chain, *S–S* disulfide bond). (**b**) The 150 kDa core neurotoxin (blue colored) and surrounding complexing proteins (brown colored) (photo, courtesy of Merz Korea)