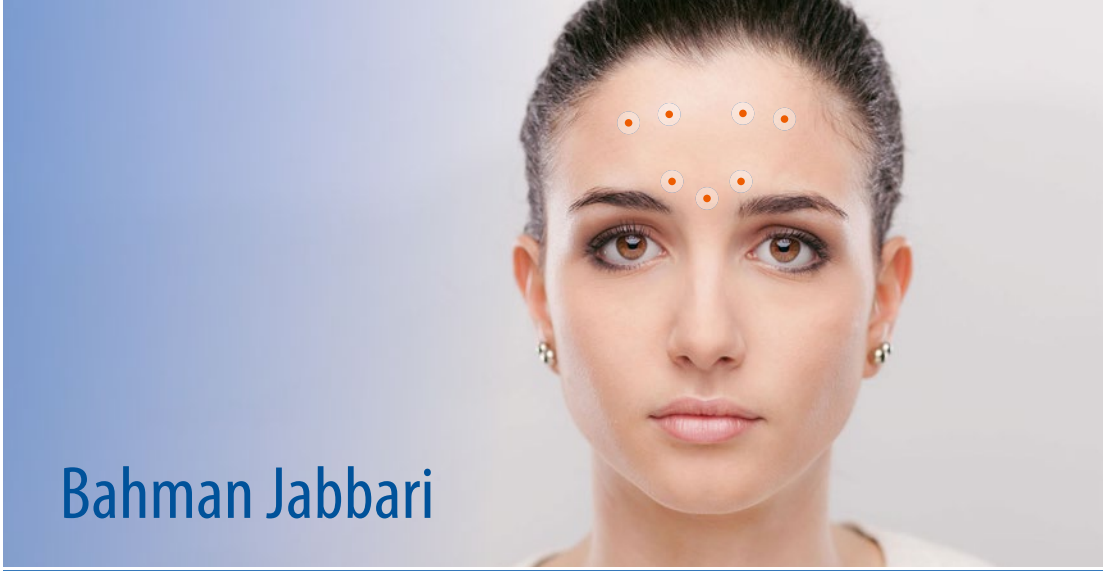

Bahman Jabbari

Botulinum Toxin Treatment

What Everyone Should Know

Springer

Botulinum Toxin Treatment

Bahman Jabbari

Botulinum Toxin Treatment

What Everyone Should Know

Springer

Bahman Jabbari
Emeritus Professor of Neurology
Yale University School of Medicine
New Haven, CT, USA

ISBN 978-3-319-99944-9 ISBN 978-3-319-99945-6 (eBook)
https://doi.org/10.1007/978-3-319-99945-6

Library of Congress Control Number: 2018957314

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Fattaneh

Preface

One of the most remarkable medical achievements in the late twentieth century was the introduction of botulinum toxin therapy to clinical medicine. The notion that a potent toxin, capable of causing a serious illness such as botulism, could remedy symptoms of diverse medical conditions was unimaginable until then. The credit goes to the American scientists who in 1940s and 1950s purified and produced this bacterial toxin in an injectable form, Dr. Allen Scott who had the vision to see its clinical utility in 1960s and 1970s, and to the tireless work of researchers from Columbia University in New York and Baylor Medical College in Houston, whose earlier contributions opened the window for many clinical discoveries in this field. Currently, botulinum toxin therapy is the first line of treatment for several dystonias and facial spasms. It is also commonly and effectively used for treatment of chronic migraine, spasticity and bladder dysfunction resulting from such common conditions as stroke, multiple sclerosis, and brain or spinal cord injury.

As a clinician and researcher who has worked in this field since its inception (1989), it became increasingly evident to me that with the current diverse applications of botulinum therapy in medicine, a book that explains its utility in a simple language would be of value to the general public. This book, reflecting the current literature and my own experience over the past nearly 30 years in the field, intends to provide the public with this information. In the first two chapters of the book, I have tried to describe, in a simple language, the molecular structure of the toxin and its different mechanisms of action responsible for improving patients' symptoms. Chapter 3 describes different types of the toxins that are currently available in the US market (Botox, Xeomin, Dysport and Myobloc), their similarities, and differences. Chapters 4 through 16 discuss the current utilization of botulinum toxin in management of the different disorders (stroke, multiple sclerosis, etc.). In Chap. 12, Drs. Grunzweig and Totonchi discuss the role of botulinum toxin therapy in plastic surgery. Chapter 17 covers the new perspectives.

I like to express my gratitude to Carolyn Spence from Springer for her continued support and encouragement. I am indebted to Drs. Tahere Mousavi and Damoun Safarpour who provided illustrations for this book and to Fattaneh Tavassoli, M.D., for her invaluable editorial assistance.

Newport Coast, CA, USA Bahman Jabbari
July 14, 2018

Contents

Chapter 1
A Neurotoxin Which is Used for Health – How it all Began?

Introduction

A group of bacterial toxins called botulinum toxins or botulinum neurotoxins have now become a remedy for a large number of hard to treat medical conditions. They have proven to be the most multipurpose therapeutic agents in modern medicine and possess more clinical applications than any other drug currently in the market [1]. Among these toxins, one type (type A) was first introduced to the medical arena in 1989 under the trade name of oculinum (name changed to Botox 2 years later). It has been the only approved toxin in the US for several years. There are now several other type A botulinum toxins and a type B toxin, each with their advantages and disadvantages. Three decades of experience with botulinum toxin therapy indicates that these agents can be drugs of first choice for the symptoms of several medical conditions, and when used by trained clinicians, are generally safe. Serious side effects are rare and in most cases gradually subside and, the affected patients survive if medically supported.

Botulinum neurotoxin, often abbreviated in the medical literature as BoNT, is produced by a bacteria with the medical name of clostridium botulinum (CB). The bacteria, CB, is present in nature and improper exposure to it can cause a disease called botulism. The term botulinum comes from the Latin word of "botulus" meaning sausage since the earlier outbreaks of botulism in Europe (eighteenth and nineteenth century) were often linked to consumption of spoiled sausage or ham. The agent can get into the body and cause disease via a variety of routes: food consumption, inhalation, wound contamination and injection. In western countries, botulism is rare due to proper food preparation, wound hygiene and protective laboratory regulations (preventing inhalation toxicity). Botulism through therapeutic injections is also rare as the applied units of the toxin for most indications are below 500 units which is far from the lethal dose of 3000 units or more reported in monkeys [2]. Moreover, with modern and advanced life support facilities, even very sick patients

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_1

with respiratory failure often eventually recover as the paralyzing effect of the toxin will not last more than 3–4 months.

The development of a therapeutic utility of BoNT took over a 100 years of clinical observation and laboratory experimentation. As mentioned above, physicians in Europe, especially in southern Germany, were familiar with the symptoms of a disease which was caused by sausage "poisoning." After a well- documented outbreak of sausage "poisoning" in 1793 that affected 13 individuals - 6 of whom did not survive-, the city of Stuttgart became the major center for investigation of this type of poisoning [3]. At the beginning of the nineteenth century, a leading point of debate was whether the "sausage poisoning" was due to a chemical agent in the sausage or due to a biologic, yet unknown, factor. Several chemical agents were suspected including hydrocyanic acid.

The next major development was the prediction that the agent responsible for "sausage poisoning" could be used for treatment of symptoms of certain medical ailments. The individual who first promoted the idea was a young German physician, 29 years of age at the time, who studied in detail the latest outbreaks of the illness in southern Germany (Fig. 1.1). Justinus Kerner published two monographs in 1820 and 1822 detailing the clinical aspects of botulism based on case histories of 76 and 155 patients, respectively [4]. Kerner's descriptions included almost all

Fig. 1.1 Justinus Kerner, drawn by Muller in early nineteenth century. He studied in detail the symptoms of botulism and predicted that the "poison" in the rotten sausage had a potential for future medical use

manifestations of botulism, as known to us today, including paralysis of the muscles, loss of pupillary reaction to light and diminished sweat and saliva production. After studying all ingredients of the poisoned food, he concluded that something in the fatty portion of the sausage itself and not any other ingredients in the sausage preparation (blood, liver, etc) was responsible for the sickness. Kerner believed that this "fatty poison" had a biological rather than a chemical origin. He wrote that the toxic agent had to travel through the nervous system to cause paralysis and the other symptoms of the disease. The toxin damaged the nerves and made them like "rusted electrical wires".

Kerner predicted that the "sausage poison" could be used in the future to remedy certain symptoms of some medical disorders, particularly those symptoms arising from hyperexcitability of the nervous system that resulted in abnormal movements. He mentioned treatment of the involuntary movement of "chorea" as an example. Chorea is a movement disorder characterized by involuntary twitches which can affect the face or the limbs. Chorea may be hereditary (i.e. Huntington's chorea) or it may develop secondary to non-hereditary diseases or drugs. Currently, almost 200 years after Kerner's prediction, medicinal botulinum toxin injections have become the therapy of first choice for many movement disorders, interestingly, however, it is least used in management of chorea – the movement disorder that he used as an example.

In 1895, Emile Van Emengem, a professor of bacteriology at the University of Ghent, Belgium discovered the organism responsible for botulism (Fig. 1.2).

Fig. 1.2 Emile Van Ermengem Photographic reproduction of art work

He had studied the rotten ham consumed by a group of 34 musicians who all felt sick after an outgoing. He showed that the spoiled ham and the tissue obtained from 3 patients who did not survive, contained a large number of rod–shaped, gram positive bacteria (Fig. 1.3). Van Emengem published a detailed account of his finding in 1897 naming the discovered bacteria, bacillus botulinum.

In 1919, G.Burke at Stanford University defined two main serological types for the botulinum neurotoxin namely type A and B toxins. In 1924, Ida Bengstrom a Swedish-American bacteriologist, suggested to substitute the name bacillus botulinum by clostridium botulinum. The genus clostridia includes a number of anaerobic (not needing oxygen) bacteria such as those responsible for production of the tetanus toxin. The word clostridium is derived from the Greek word of Kloster meaning spindle.

Further refinement of the botulinum toxin which ultimately facilitated its clinical use, came about during World War II when there was an interest in producing large amounts of the toxin and to find preventive and therapeutic measures in case of exposure and intoxication. Close to the end of World War II, at Fort Detrick Maryland, at a US Army research facility, Carl Lamanna and James Duff invented a technique for crystallization and concentration of botulinum toxin [2]. Edward Schantz (Fig. 1.4), purified and produced the first batch of the toxin in 1946. Shantz then moved to the University of Wisconsin where with Eric Johnson further refined the botulinum toxin for clinical research.

In 1949, a British investigator, A. Burgen, and his colleagues discovered that botulinum toxin blocks the nerve transmitter substance "acetylcholine" at nerve-muscle junction leading to the toxin's paralytic effect. In 1964, Daniel Drachman at Johns Hopkins University demonstrated that injection of the type A botulinum toxin (BoNT-A) into the muscles of chick embryos can produce a dose dependent muscle wasting (atrophy) and muscle weakening [5].

The next major step started with the work of Alan Scott and his colleagues in San Fransisco, CA. Since early 1960s, Alan Scott, an ophthalmologist, and his colleague

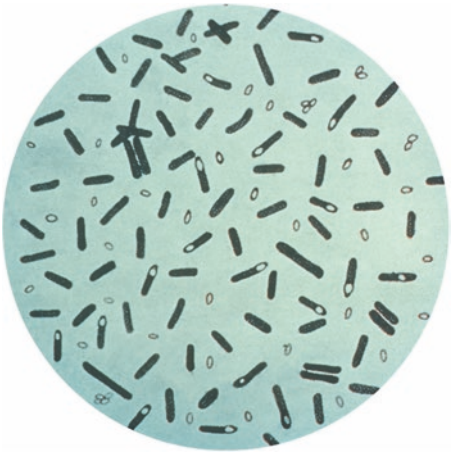

Fig. 1.3 Rod-shape gram positive bacteria, clostridium botulinum

Fig. 1.4 Edward Shantz an Eric Johnson in the laboratory at the University of Wisconsin. From Dressler & Roggenkeaemper. Reproduced with permission from Springer

Carter Collins were interested in the physiology of eye muscles and correction of strabismus (crossed eyes) in children by a method other than resection of muscles around the eye. Their research focused on injection of anaesthetic agents into these muscles in monkeys under electromyographic guidance. Electromyography records the electrical activity of muscles through a special instrument. Coming across Drachman's work, Dr.Scott started to explore the effects of botulinum toxin injections into the eye muscles of the monkeys. Edward Schantz who was then at University of Wisconsin, provided the purified and injectable toxin for Dr.scott's experiments. In Scott's laboratory, the toxin was freeze-dried, buffered with albumin and prepared for injection in small aliquots.

In 1973, Dr. Scott published his seminal work on injection of botulinum toxin type A into the external eye muscles of the monkeys. The work clearly showed that the toxin injection can selectively weaken a targeted eye muscle and offer an alternative to surgery for strabismus. His subsequent work on 67 patients with strabismus (under an FDA approved protocol), published in 1980, demonstrated that indeed botulinum toxin injection was effective in correcting human strabismus [6]. Dr.Scott also showed, in a number of open label, unblinded studies, that injection of botulinum toxin into face muscles of humans can slow down and even stop involuntary facial movements in conditions like blepharospasm (spasm of the eye lids) and hemifacial spasm (involuntary contractions affecting half of the face). These observations ignited substantial interest among Movement Disorder specialists and consequently led to documentation of the efficacy of BoNT therapy for a large number of involuntary movements. Finally, his observation in spasticity (tense muscle with increased tone due to brain and spinal cord damage) that injection of 300 units in humans did not cause any side effects, indicated a margin of safety of at least 300 unit per single injection of botulinum toxin type-A in human which was unknown prior to his observation [2] (Fig. 1.5).

Dr.Scott's efforts along with the work of Stanley Fahn and Mitchell Brin at Columbia University of New York and Joseph Janckovic at Baylor Medical College and Joseph Tsui at British Columbia led to the approval of botulinum toxinA (then

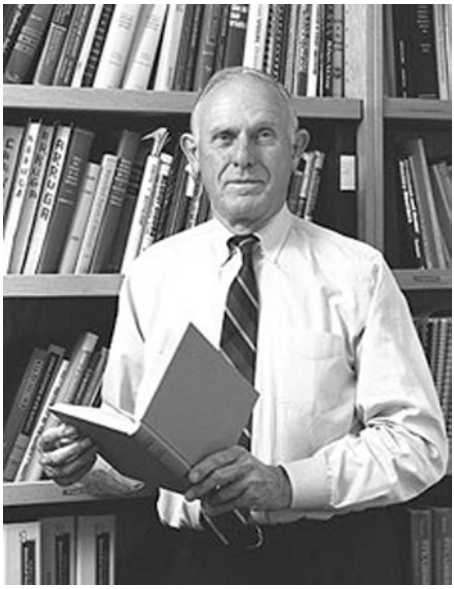

Fig. 1.5 Alan Scott who pioneered the use of botulinum neurotoxin therapy in humans. From FJ Erbguth in the J. Neural Trans- Reproduced by permission from Publisher-Springer

called oculinum, marketed by Allergan- the name was changed to Botox 2 years later) for treatment of strabismus, blepharospasm and hemifacial spasm in 1989. The path was now open for investigation of the effects of BoNTs in many other movement disorders and many other symptoms in the medical field.

What happened over the next 29 years is one of the most amazing stories in the field of medical treatment. A potent bacterial toxin which was the cause of much fear and apprehension developed into a therapeutic agent with documented or highly suggestive efficacy in alleviating more than 100 medical symptoms. It was found to be generally safe if used with proper techniques of injection and under appropriate dosing guidelines. Much was learned during these years about the molecular structure of botulinum toxins [7], and their mode of action(s) on the nerve-muscle junction (Chap. 2), glandular tissue [8], and pain pathways [9].

Besides Botox, two more botulinum neurotoxin type-As were developed and subsequently marketed in the US under the trade names of Xeomin and Dysport. Much of the work in Europe was done by the leading investigators Dirk Dressler and Reiner Benecki and their collaborators who were also instrumental in designing many European studies of Dysport and Xeomin [10]. A type B toxin was also marketed in the US with the trade name of Myobloc (Neurobloc in Europe). Much was learned about the advantages and disadvantages of these toxins over time (detailed description are given in Chap. 3 of this book).

Encouraged by earlier promising results, knowledgeable investigators with innovative minds conducted careful, high quality, double blinded clinical trials. The results of these multicenter studies which were conducted with sizeable number of patients led to FDA approval to use Botox for a variety of medical conditions. In 2002, FDA approved injections of Botox into the face for correction of wrinkles

(Chap. 12) and in 2004 approved Botox for treatment and reduction of excessive sweating arm pit (axilla) (Chap. 14). In 2009, FDA also improved Botox injections for treatment of a disabling movement disorder characterized by abnormal neck posture, neck pain and neck shakes (Cervical dystonia-Chap. 11)). Botox was approved for two types of bladder dysfunction in 2011 and 2013 (Chap. 8). As research continued, positive results of two large multicenter studies (PREEMPT 1 & 2) which showed efficacy of Botox injections into the skin and muscles around the head in subjects with chronic migraine (migraine headaches of 15 or more days per month), led to the FDA approval of Botox for treatment for this disabling condition (Chap. 4). The next notable event in the string of FDA approvals was approval for the very common symptom of spasticity (tense and contracted muscle), a major handicap for patients with stroke, multiple sclerosis and other brain and spinal cord injuries as well as among children with cerebral palsy. FDA approved Botulinum toxin treatment of upper limb spasticity in 2010 and lower limb spasticity in 2014 (Chaps. 7 and 8). It should be noted that FDA approval for several of aforementioned indications (cervical dystonia, excessive sweating, spasticity) included toxins other than Botox as well (Xeomin, Dysport, Myobloc).

In addition to these FDA approved medical indications, there are approximately twenty other symptoms that have been shown to be responsive to BoNT injections via the results of well designed, blinded and high quality studies. Among these, most of the high quality studies have been conducted in the area of pain (Chap. 5) [11]. It has been shown that injection of BoNTs into or under the skin and/or into muscles results in significant alleviation of pain due to the blocking effect of BoNTs upon pain transmitters and reduction of local inflammation (Chap. 5). Other well designed blinded clinical trials have shown improvement of hand tremor after injection BoNTs into the involved muscles (Chap. 11) [12, 13]. This wide range of BoNT applications for treatment of different medical symptoms, reflects multiple and diverse mechanisms of BoNT action - covered in more detail in the second chapter of this book.

Chapters 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16 of this book cover the utility of BoNT therapy in migraine, other pain disorders, stroke symptoms, multiple sclerosis, bladder problems, abnormal movements such as dystonia and spasms, Parkinson's disease, indications for beauty and aesthetics, excessive sweating and drooling as well as safety and insurance issues.

In the final chapter of this book (Chap. 17), some of the future potential therapeutic uses of BoNTs are discussed. Some of these potential applications include treatment of irregular heartbeats (atrial fibrillation) by BoNT injection into the fat pads of the heart, alleviating the local cancer related pain and cancer related glandular dysfunction by local BoNT injection and in the field of psychiatry, improvement of depression after receiving BoNT injections into facial and forehead areas.

It is expected that continued medical research and clinical observations will further expand the clinical indications of botulinum toxin therapy as depicted in recent publications [14]. Improvement of the results of botulinum toxin therapy is also expected with refinement of injection techniques and definition of more appropriate doses for each indication (Table 1.1).

Table 1.1 Important timelines of Botulinum toxin (BoNT) development for clinical use

Year	Investigator(s)/FDA approvals	Comment
1895	Eric van Ermengem	Discovery of the bacteria causing botulism
1920–1922	Justinus kerner	Describes details of botulism- predicts the toxin can be used in the future as medical remedy
1944–1946	Lamanna and Duffy	Concentrate and crystalize the toxin
1946	Edward Schantz	Produced the toxin I na form suitable medical research
1949	A Burgen	Acetylecholine identified as the chemical blocked by BoNT at nerve muscle junction
1953	Daniel Drachman	Intramascular injection Schantz's toxin can be quantified and causes dose dependent muscle weekness in chicks.
1973	Alan Scott	Injection of type A toxin improves strabismus in monkeys
1980	Alan scott	Wider spectrum of use in human: strabismus, blepharospasm, hemifacial spasm, spasticity
1985–1988	Fahn, Brin, Jankovic, Tsui	Controlled and blinded studies show efficacy in Blepharospasm and cervical dystonia
1989	Initial FDA approval of Type A toxin (oculinum/ Botox)	Blepharospasm,hemifacial spasm and strabismus
1989-present	FDA approved other indications	Facial wrinkles, excessive arm-pit sweating, cervical dystonia, chronic migraine, bladder dysfunction, upper and lower limb spasticity, exessive drooling

References

1. Jankovic J. Botulinum toxin: state of the art. Mov Disord. 2017;32:1132–8.
2. Scott A. Development of Botulinum toxin. Forward (xi–xii). In: Jankovci J, Albanese A, Atassi MZ, Dolly JO, Hallett M, Mayer NH, editors. Botulinum toxin. Therapeutic clinical practice and science. Philadelphia: Saunders-Elsvier Publisher; 2009.
3. Erbguth F, Naumann M. Hisorical aspects of boyulinum toxin: Justinus Kerner (1786–1862) and the sausage poison. Neurology. 1999;53:1850–3.
4. Erbguth F, Ergbuth FJ. From poison to remedy: the chequered history of botulinum toxin. J Neural Transm. 2008;115:559–65.
5. Drachman DB. Atrophy of skeletal muscles in chick embryo treated with botulinum toxin. Science. 1964;145:719–21.
6. Scott A. Botulinum toxin injections into extraocular muscles as an alternative to strabismus surgery. Ophthalmology. 1980;87:1044–9.
7. Pirrazzini M, Rossetto O, Elopra R, Montecucco C. Botulinum neurotoxins: biology, pharmacology, and toxicology. Pharmacol Rev. 2017;69:200–35.
8. Hosp C, Naumann M, Hamm H. Botulinum treatment of autonomic disorders: focal hyperhidrosis and sialorrhea. Semin Neurol. 2016;36:20–6.
9. Matak I, Tékus V, Bölcskei K, Lacković Z, et al. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;358:137–45.

10. Dressler D, Roggenkaemper P. A brief history of neurological botulinum toxin therapy in Germany. J Neural Transm. 2017; https://doi.org/10.1007/s00702-017-1762-3.
11. Jabbari B. Botulinum toxin treatment of pain syndromes. New York: Springer; 2015.
12. Jankovic J, Schwartz K, Clemence W, et al. A randomized, double blind, placebo controlled study to evaluate botulinum toxin type A in essential hand tremor. Mov Disord. 1996;11:250–6.
13. Shivam OM, Machado D, Richardson D, et al. Botulinum toxin treatment in Parkinson disease tremor. A randomized placebo controlled, double blind study with customized injection approach. Mayo Clin Proc. 2017;92:1359–67.
14. Jabbari B, editor. Botulinum toxin treatment in clinical medicine- a disease oriented approach. New York: Springer; 2018.

Chapter 2
Basics of Structure and Mechanisms of Function of Botulinum Toxin - How Does it Work?

Introduction

Botulinum toxin or botulinum neurotoxin (BoNT) is a protein which is produced by a bacteria named clostridium botulinum. The term clostridium refers to the shape of the bacteria which is spindle/rod shaped and the term botulinum is derived from the Greek word of botulus (sausage) since earlier outbreaks of botulism were related to the consumption of rotten sausage. The history of early botulism outbreaks, discovery of the responsible agent, purification and production of the toxin for medical research as well as early clinical trials which led to discovery of BoNT's effectiveness in treatment of medical disorders are presented in detail in Chap. 1. This chapter focuses on an explanation of how this toxin work.

The results of animal research and early human observations which emerged during 60s and 70's, indicating a significant therapeutic potential for BoNT, encouraged basic scientists to explore the molecular structure of the toxin and its mode of action. These efforts succeeded to decipher the exact molecular structure of BoNT and provide a large amount of knowledge about how the toxin molecule reaches the nerves and exerts its therapeutic action after it is injected into the site of concern.

Botulinum toxin is structurally a protein with perfect machinery to exert its function through a set of well –defined mechanisms. There are 7 distinct types of botulinum toxins (A,B,C,D,E,F,G) that are structurally similar with only minor differences. Types A, B,E and F can cause botulism in human, whereas, types C and D mainly cause botulism in domestic animals [1]. Recently, several subtypes have been discovered (A1, A2,…) [2]. Continued research efforts are underway to define the role of these subtypes. Currently, only types A and B are suitable for clinical use.

Botulinum toxin molecule (type A) is an approximately 900 KiloDalton (KD) complex which consists of a core toxin (150KD) and a complex of surrounding proteins (>700 KD). Dalton the unified atomic mass unit, is a standard unit of mass that quantifies mass on an atomic or molecular scale. The surrounding proteins of the core toxin protect the toxin from being degraded in a hostile environment such

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_2

as acid of the stomach after its ingestion. However, when the BoNT is injected into a muscle, the tissue enzymes (protease) quickly separate the toxin from the surrounding proteins by a process termed "nicking". The core toxin molecule then reaches its target at nerve endings probably via blood or lymphatic system [3].

The point where a nerve connects to a muscle is called neuromuscular junction. The point where the end of a nerve (nerve terminal) contacts a muscle is also called synapse in medical terms. In case of nerve-muscle synapse, the synapse has a membrane on the nerve side and a membrane on the muscle side with a cleft in between (synaptic cleft) (Fig. 2.1). The nerve ending close to the muscle contains many small vesicles that contain a chemical called neurotransmitter. When nerve's electrical signals reach the nerve ending the vesicles rupture and pour their neurottansmitter contents into the synaptic cleft . The neurotransmitter then attaches itself to the muscle membrane and activate (contracts) the muscle. The neurotransmitter in the nerve-muscle junction is a chemical called acetylcholine. Injected Botulinum neurotoxins can relax, weaken or even paralyze the muscle (depending on the dose) by preventing release of acetylcholine from the synaptic vesicles. The mechanism through which BoNT exerts its effect on nerve-muscle junction is complex and requires some knowledge of core toxin's molecular structure.

Each molecule of the toxin consists of two structures, called light chain (50 KD) and heavy chain (100 KD). KD stands for kilodalton. Dalton is the unit of atomic weight. These two chains are connected by a disulfide bond (Fig. 2.2).

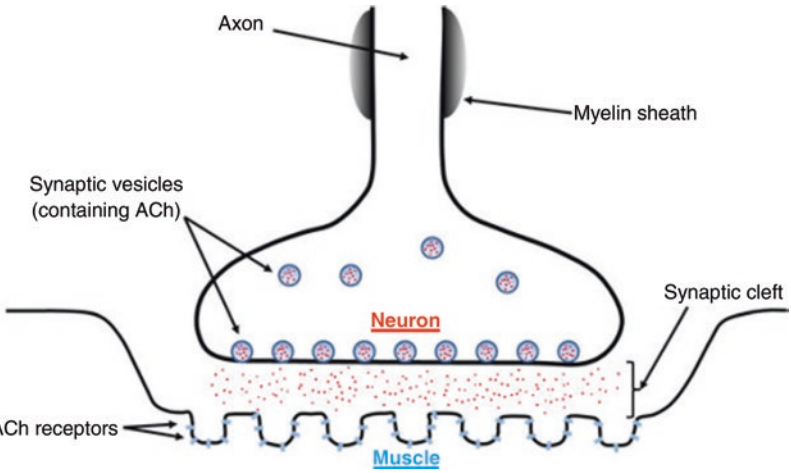

Fig. 2.1 Neuromuscular junction: Nerve and nerve terminal, muscle fiber, and synaptic cleft between. Nerve terminal shows vesicles that contain the neurotransmitter acetylcholine. Nerve signals reaching the nerve terminal at neuro-muscular junction lead to rupture of the vesicles and release of acetylcholine molecules into the synaptic cleft. Acetylcholine molecules attach to muscle receptors on the surface of the muscle and activate the muscle

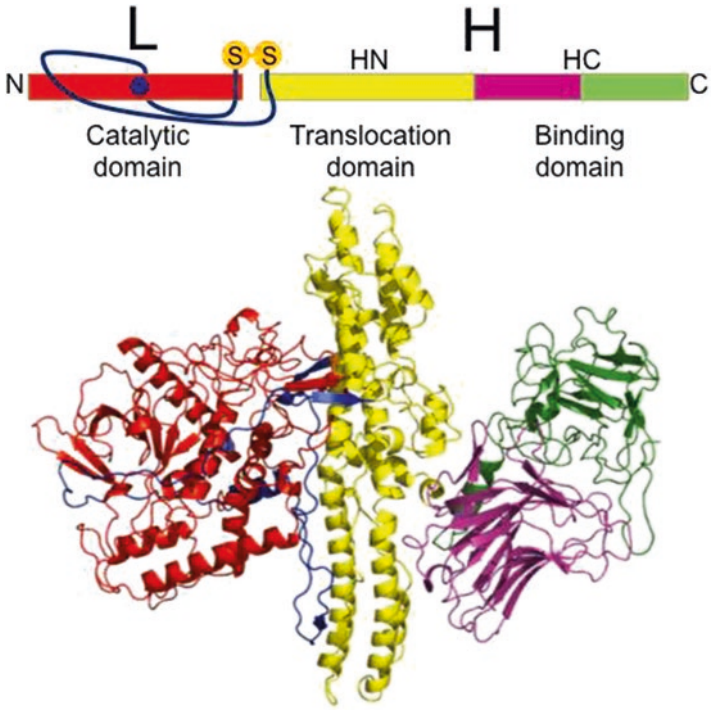

Fig. 2.2 Molecular structure of botulinum toxin. From Rossetto O (2018), in Botulinum toxin Treatment in Clinical medicine (Jabbari B -Editor) . Reproduced by permission from Publisher-Springer

The light chain, the catalytic domain, is the active moiety of the toxin. The heavy chain has two parts called HC and HN domains (Fig. 2.2). The HC domain (binding domain) attaches the toxin to the membrain receptors of the nerve cell. There are specific receptors on the nerve cell membrane that the HC domain of the toxin can attach itself to. The receptor for type A toxin is a protein called SV2. For type B toxin, two receptors have been identified a ganglioside (a form of complex sugar) and a protein called synaptogamin. After the toxin attaches to the receptor, the receptor undergo structural modification and works like a channel letting the toxin go through. The HN domain (translocation domain) of the toxin then moves the whole toxin molecule inside the nerve cell terminal through the chanelled receptor. After entering the nerve terminal, the disulfide bond of BoNT breaks and the two chains of the toxin separate from each other. The light chain (active moiety of the toxin) is now free to exert its effect and prevent the release of acetylcholine from the synaptic vesicles. It does this via attaching itself to specific synapse proteins whose function is to promote the fusion of the vesicle onto the nerve membrane. Vesicle fusion to the synapse membrane leads to its rupture and release of the neurotransmitter, acetylcholine into the synaptic cleft. The synapse proteins that promote vesicular fusion and rupture are called SNARE (Soluble NSF Attachment Protein).

Over the past 30–40 years, a group of cell biologists succeeded to determine the mechanisms of vesicle fusion and synaptic machinery including the function of SNAREs. [4] Most notable among these scientists are J.Rothman, R.Schekman and TC.Sudhof who won the Nobel prize in Medicine & Physiology in 2013 for their work in this area, (Fig. 2.3).

While inside the nerve terminal and detached from the heavy chain, the light chain of the BoNT attaches itself to a specific SNARE that attracts that specific type of the toxin (for instance type A or B). After attachment to the SNARE protein the light chain of the toxin deactivate the SNARE protein via light chain's enzymatic function (a Zinc activated protease). The result is inhibition of release of the neurotransmitter from the vesicle and, in case of nerve-muscle synapse, relaxation, weakness or even paralysis of the muscle depending on the dose of the injected toxin. The SNARE for Type A toxins (Botox, Xeomin, Dysport) was first discovered by a group of Yale investigators and named SNAP 25. [5] It is attached to the membrane of the nerve terminal. For the type B toxin, the SNARE is attached to the vesicle wall itself and is designated as Synaptobrevin. (Table 2.1)

The binding of the BoNTs A and B to the nerve terminal is a long-term binding that in case of nerve- muscle junction lasts for 3–4 months [6]. This long period of binding is medically desirable. For instance in spastic and tense muscles of patients with stroke or children with cerebral palsy, one injection could maintain the muscle relaxation for the entire period of binding. Over time, the nerve ending starts to sprout and the new endings make contact with different muscle fibers. Finally when the binding is over the synapse resumes its full function. This reversibility which is the hallmark of BoNT function is very different from the disease conditions that often destroy the synapse and lead to neurodegeneration and often perment loss of function.

Fig. 2.3 Dr. James Rothman, Yale Cell biologist who won the Nobel prize in physiology and Medicine in 2013 for his work on physiology of the synapse

Table 2.1 Sequence of Botulinum toxin action after injection into the muscle

1.	After injection in to the muscle, protease, an enzyme inside the muscle separates the core toxin from protective proteins around the core toxin
2.	The released toxin molecule reaches nerve muscle junction probably via blood or lymphatic system
3.	Heavy chain of the toxin attaches the toxin molecule to certain receptors on the surface of terminal nerve ending (SV2 for Botox)
4.	Receptors open as a channel and let the toxin molecule enter into the nerve terminal
5.	The disulfide bond of the toxin break inside of the nerve terminal via function of heavy chain
6.	Freed light chain of the toxin (active or catalytic moiety) reaches the SNARE proteins and deactivate them via its enzymatic function
7.	Deactivation of SNARE protein prevents rupture of synaptic vesicles and release of acetylcholine
8.	Muscle deprived from acetylcholine activation relaxes and slightly weakens, an effect that improves muscle spasms, abnormally high muscle tone (spasticity) and involuntary movements.

Excessive Sweating and Drooling

The nerves exciting sweat, tear and salivary glands originate from the sympathetic nervous system. Acetylcholine is also the neurotransmitter for the sympathetic nerve endings that supply nerves to sweat and salivary glands. BoNT injections into and under the skin in the areas where these glands are located (for instance arm pit, hands and feet for sweat glands or face for salivary glands) effectively reduces sweating and drooling (Chap. 13 of this book). The injections can be very helpful in patients with excessive sweating on the hands or feet or at the arm pit. Also patients with excessive drooling may do well when botulinum toxins (type A or B) are injected into the salivary glands. The parotid glans is just under the skin above the angle of the jaw and the submandibular glands are under the jaw at the junction of medial one third and lateral two third. For reasons which are not yet well understood, effects of BoNT over sympathetic nerves controlling salivation and drooling lasts longer than that observed in nerve-muscle junction (usually 6 months, and in some cases as long as a year, after one injection). The molecular mechanism of blockage of sweat, tear and saliva secretion is similar to that provided for the nerve-muscle junction.

Pain

This a relatively new area of BoNT indication. For migraine, the efficacy of BoNT-A (Botox) has been proven by several high quality studies [7] and Botox was approved for use in treatment of chronic migraine by FDA (2010) in the US. Further studies

have shown that BoNTs are effective in a number of other pain syndromes [8] (Chaps. 4 and 5 of the book). In case of pain, the molecules of Botox exert their effect on the sensory nerve fibers through a similar cascade of mechanisms. Animal studies have shown that injection of Botox into the muscle (intramuscular) or under the skin can block the release of several well recognized pain transmitters such as glutamate, substance P and Calicitonin gene-relater peptide (CGRP). These agents accumulate in peripheral nerve endings in reaction to noxious peripheral stimulation and through their action the abnormal sensation invoked in the peripheral nerves is conveyed to the brain and perceived as pain. Blocking the release of pain transmitters from peripheral nerve endings reduced sensitization of peripheral nerve endings and alleviates pain.

More recently, an additional "central" mechanism for the action of botulinum toxin molecules on pain has been elucidated based on animal studies. The support for a central (spinal cord and possibly brain) mechanism comes from several lines of research, two of which are described below:

1- Direct application of BoNT to dura matter (the brain covering) alleviated facial pain and reduced the inflammation caused by experimentally induced pain (ligation of a facial nerve) in laboratory animals. [9]
2- In an animal model of leg pain caused by diabetic neuropathy (nerve damage due to diabetes) injection of BoNT into one leg, not only reduced the pain in that leg but also in the other leg implying an analgesic function through a spinal cord loop with participation of spinal cord nerve cells [10].

These central mechanisms, however, do not seem to exert any deleterious effect on the spinal cord or brain (in doses approved for clinical use) since millions of patient who receive BoNT injections every year do not complain of any untoward side effects related to central nervous system.

Recently, scientists have succeeded in making a toxin molecule consisting of combination of two toxins (chimera- for instance for instance E/A toxins), that can specifically target the sensory nerve cells and hence specifically treat pain [11]. It remains to be seen how effective these chimeric molecules will work in human and in clinical practice.

The details of Botulinum Neurotoxins: Biology, Pharmacology, and Toxicology can be found in a recently published comprehensive review. [12]

References

1. Rossetto O. Chapter 1: Botulinum toxins: Molecular structures and synaptic physiology. In: Jabbari B, editor. Botulinum toxin treatment in clinical medicine-a disease oriented approach. New York: Springer; 2017. p. 1–12.
2. Monteccuco C, Rasso MB. On botulinum neurotoxin variability. MBio. 2015:6e02131.
3. Lacy DB, Tepp W, Cohen AC, DasGupta BR, Stevens RC. Crystal structure of botulinum neurotoxin type A and implications for toxicity. Nat Struct Biol. 1998;5:898–902.

4. Rothman JE. The principle of membrane fusion in the cell (Nobel lecture). Angew Chem Int Ed Engl. 2014;53(47):12676–94. https://doi.org/10.1002/anie.201402380.Epub2014A.
5. Blasi J1, Chapman ER, Link E, Binz T, Yamasaki S, De Camilli P, Südhof TC, Niemann H, Jahn R. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. Nature. 1993;365(6442):160–3.
6. Kumar R, Dhaliwal HP, Kukreja RV, Singh BR. The botulinum toxin as a therapeutic agent: molecular structure and mechanism of action in motor and sensory systems. Semin Neurol. 2016;36:10–9.
7. Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, VanDenburgh AM, Nolan ME, Turkel CC. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache. 2011;51:1358–73.
8. Jabbari B. Botulinum toxin treatment of pain disorders. New York: Springer; 2015.
9. Lacković Z, Filipović B, Matak I, et al. Activity of botulinum toxin type A in cranial dura: implications for treatment of migraine and other headaches. Br J Pharmacol. 2016;173:279–91.
10. Bach-Rojecky L, Salković-Petrisić M, Lacković Z. Botulinum toxin type A reduces pain supersensitivity in experimental diabetic neuropathy: bilateral effect after unilateral injection. Eur J Pharmacol. 2010;633:10–4.
11. Wang J, Casals-Diaz L, Zurawski T, et al. A novel therapeutic with two SNAP-25 inactivating proteases shows long-lasting anti-hyperalgesic activity in a rat model of neuropathic pain. Neuropharmacology. 2017;118:223–32.
12. Pirrazzini M, Rossetto O, Elopra R, Montecucco C. Botulinum neurotoxins: biology, pharmacology, and toxicology. Pharmacol Rev. 2017;69:200–35.

Chapter 3
Botox and Other Neurotoxins

Introduction

The history of botulinum neurotoxin (BoNT) and how it developed and evolved from a lethal toxin to a widely used and relatively safe medical agent has been discussed in Chap. 1 of this book. In Chap. 2, the molecular structure and mechanisms of function of botulinum toxins were discussed. This chapter (Chap. 3), defines the qualities and characteristics of four FDA approved types of botulinum toxin currently used in US. These are Botox, Xeomin, Dysport and Myobloc (Fig. 3.1).

Of seven subtypes of botulinum toxins (see Chap. 2), only type A and B are used for treatment in clinical medicine due to their prolonged action and suitability for medical use. Botox, Xeomin and Dysport are type A; Myobloc is a type B toxin. In medical communications and research manuscripts, usually the trade names are avoided, and proprietary names are used instead (Table 3.1). Two other type A toxins are used widely in Asia, but they are not approved by FDA for use in the US (Table 3.1). FDA has provided proprietary names for the 4 botulinum toxins that are approved in US (Table 3.1).

There is difference between these toxins in term of preparation, dilution, refrigeration, unit potency and immunogenicity. These differences are summarized in Table 3.2 and discussed in more detail below.

Botox (Allergan Inc., Irvine California)

Botox is the first botulinum toxin marketed for clinical use. It was initially introduced in 1989 under the trade name of oculinum (related to the eye) since that time, the focus was on eye related indications such as strabismus (squint) and abnormal movements around or close to the eyes (blepharospasm and hemifacial spasm). Two years later, noticing the wide potential application of the toxin in the medical field,

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_3

Fig. 3.1 Four FDA approved botulinum toxins, three type A (Botox, Xeomin, Dysport) and one type B (Myobloc). From Chen and Dashtipour 2013 [1] - With permission from Publisher (Wiley and Sons)

Table 3.1 Six commonly used botulinum toxins -Trade name, generic name, manufacturer, FDA status

Trade name	Proprietary name	Abreviation	Manucacturer	FDA approved
Botox	onabotulinumtoxinA	onaBoNT-A or onaA	Allergan -Inc	Yes
Xeomin	incobotulinumtoxinA	incoBoNT-A or incoA	Merz Pharmaceutical	Yes
Dysport	abobotulinumtoxinA	aboBoNT-A or aboA	Ipsen pharmaceutical	Yes
Myobloc[a]	rimabotulinumtoxinB	rimaBoNT-B or rimaB	US WorldMed-Solstice	Yes
Proscine	–	Type A	Lanzhou Institute, China	No
Meditoxin (inotox)	–	Type A	Medytox South Korea	No

[a]Marketed as Neurobloc in Europe, BoNT: botulinumneurotoxin

Table 3.2 Trade name, preparation, need for refrigeration, serum albumin content, immunogenicity of botulinumneurotoxins (BoNTs)

Trade name	Preparation	Refrigeration Shelf life	Expedient	Protein load/100 units in nanogram	Approximate Unit equivalency	Immuno-Vials/Genicity Units	Vials
Botox	To be diluted with NS	Yes 2–8 degrees © 24–36 months	Human serum albumin	5 /100 units	1	Low	50 and 100 units
Xeomin	To be diluted NS	Does not need refrigeration	Human serum albumin	0.44/100 units	1	Very low	50 and 100 units
Dysport	To be diluted with NS	Yes 2–8 degrees©	Human serum albumin	4.35/500 units	2–3	Low	300, 500 and 1000 units
Myobloc	Provided as ready to use solution –does not need dilution	Yes 2–8 degrees©	Human serum albumin	55/2500 units	40–50	Low	2500, 5000 and 10,000 units
Proscine Chinese toxin from Lanzhou Institute	To be diluted with NS	Yes 2–8 degrees© (c)	Gelatin (bovine), dextrose	?	1–1.5	Low	50 and 100 units
Meditoxin (neuronox) from South Korea	To be diluted with NS-	Yes 2–8 degrees©	Human serum albumin	?	1	Low	50 and 100 units

[a]Myobloc is marketed as neurobloc in Europe
[b]Prosigne and Meditoxin are not approved by FDA
[c]BoNT: botulinumneurotoxin, NS: normal saline
[d]Immunogenicity implies potential for antibody formation against BoNT; when an immune reaction develops, it may make the toxin ineffective. From Benecke R. 2012 [2]

the name was changed to Botox. Botox is the most widely used of botulinum toxins and currently has over 80% of the US market. Botox is a type A botulinum toxin similar to the other two of its competitors, Xeomin and Dysport. Out of 7 different serotypes of the BoNTs, only types A and B have medical applications. Part of this is due to the long duration of action of these two types of BoNTs (A and B) that after a single intramuscular or subcutaneous injection, render 3–6 months action (depending on the clinical condition).

Botox is provides in small vials (Fig. 3.1) that contain 50 or 100 units of botulinum toxin. The unit of the toxin is based on toxin's lethality in mice. One unit is the amount of toxin that can kill 50% of the test population (mice).

Botox is heat sensitive. The original vial of Botox as well as prepared Botox (mixed with normal saline- salt water, before injection), needs to be kept in the refrigerator. Manufacturer recommends the prepared solution to be used within 4–6 h after reconstruction. There are studies, however, that claim, reconstructed Botox solution can maintain its potency for up to 6 weeks if kept in the refrigerator. Patients who buy Botox from the pharmacy and plan to take it to the physician's office for injection need to be particularly diligent about the issue of Botox's heat sensitivity. Botox content of the vial will lose its potency if left at room temperature for more than a few hours. If a patient buys a Botox vial today from the pharmacy and plans to go to the treating physician's office the next day, the Botox vial should be refrigerated!

Like other botulinum toxins in the market, the effect of Botox for most indications, lasts in average 3–4 months. For some indications, drooling and excessive sweating as well as bladder dysfunction (see Chaps. 8 and 13) the duration of action is longer and can even exceed 6 months. Injection of botulinum toxins, especially in large amounts (such as used for relaxing spastic limbs after stroke), can lead to formation of antibodies and some patients with antibodies (especially neutralizing antibodies) against Botox will become a non-responder. This antibody formation is related to the presence of human albumin in the Botox vial . However great improvements have been made in this regard over the past 25 years. Current Botox vials contain only 0.5 ng of human albumin with a protein load of 5 ng/100 units. This is substantially reduced from 25 ng/100 units which was present in the Botox formulations prior to 1997. The low protein load of the current Botox preparations has reduced toxin's antibody formation to less than 1.2% (from previous figure of of approximately 10%) with development of non-responsiveness down to 1% or less after repeated applications [2].

Xeomin (Merz Pharmaceuticals, Frankfurt- Germany) [3]

This is another type A botulinum toxin with activities very similar to Botox. The units of Xeomin are close to Botox in potency and in comparative clinical trials researchers often use a 1:1 Xeomin/Botox ratio. It should be remembered that the units of different botulinum toxins are never truly comparable and the given equivalents are at best an approximation.

Xeomin's structure is very similar to the South Korean toxin Meditoxin / Neurotox produced in year 2000 by the Korean Medytox pharmaceutical. Merz a German pharmaceutical company produces and distributes Xeomin in US. Although Xeomin still does not have FDA approval for some major clinical indications (migraine, bladder dysfunction) as Botox does, in other areas (dystonias, spasticity, cosmetic), it has FDA approval and possesses an efficacy comparable to Botox (Table 3.3). It is also approved for treatment of excessive sweating and drooling for which Botox does not have FDA approval (although used extensively based on a large number of supporting literature). Like Botox, Xeomin is provided in vials containing 50 and 100 units (Fig. 3.1, Table 3.3).

Xeomin has three advantages over Botox and other toxins:

1. It does not have to be refrigerated a feature that is often helpful both to patients and medical providers.
2. It has a negligible amount of albumin (protein load of 0.44 ng/100unit), hence very low antigenicity that does not lead to antibody formation. This means that the incidence of unresponsiveness even with large doses and repeated injections is extremely low (Table 3.3). In practice, however, this is a minor advantage over Botox since, as mentioned above, the new formulations of Botox have low incidence of unresponsiveness after chronic use even with large doses.
3. Reconstituted Xeomin does not show reduction of potency throughout 52 weeks and hence may make it economically more feasible than other toxins [3, 4].

Dysport (Ipsen Limited– Paris France) [5]

Dysport, a type A toxin similar to Botox, can be used for many neurological conditions (cervical dystonia, blepharospasm, hemifacial spasm, upper and lower limb muscle spasticity). Like Botox and Xeomin, it is approved by FDA for cervical dystonia and spasticity [5] treatment of excessive sweating drooling. It is the only type of botulinum toxin currently approved by FDA for treatment of lower limb spasticity in children based on high quality clinical trials (Table 3.3) [6]. Units of Dysport are different from that of Botox and Xeomin. Each 2.5–3 units of Dysport approximate 1 unit of the other two toxins. Dysport is provided in vials containing 300, 500 and 1000 units (Table 3.2).

Myobloc (Neurobloc in Europe –WorldMed/Solstice Neurosciences, Louisville, Kentucky)

Myobloc is the only type B toxin available for clinical use in US. It is approved for two indications: cervical dystonia (torticollis, laterocollis) and for autonomic disorders (excessive salivation or sweating). In cervical dystonia, a condition causing abnormal posture of the neck, there is some literature suggesting that it works better

Table 3.3 Clinical Indications approved by FDA for 4 approved botulinum toxins

Trade name	Generic name (FDA)	Abbreviation or type	Manufacturer	Approved indication (FDA)	Year of FDA approval
Botox	onabotulinumtoxinA	onaBoNT-A	Allergan -Inc	Blepharospasm	1989
				Hemifacial spasm	1989
				Strabismus	1989
				Cervical dystonia	2000
				Migraine	2010
				Upper limb spasticity	2010
				Lower limb spasticity (adult)	2014
				Bladder (NDO)	2011
				Bladder (OB)	2013
				Forehead Wrinkles	2018
Xeomin	oncobotulinumtoxinA	oncoBoNT-A	Merz Pharma	Cervical dystonia	2010
				Blepharospasm	2010
				Frown lines (aesthetics)	2011
				Upper limb spasticity	2015
				Sialorrhea (drooling) in adults	2018
Dysport	abobotulinumtoxinA	AboBoNT-A	Ipsen pharmaceutical	Cervical dystonia	2009
				Frown lines & wrinkles	2009
				Upper limb spasticity(adult)	2015
				Lower limb spasticity (children)	2016
				Lower limb spasticity (adult)	2017
				Frown lines	2009
Myobloc	rimabotulinumtoxinB	rimaBoNT-B	US World Med-Solstice	Cervical dystonia	2009
Neurobloc					

[a]Myobloc is marketed as Neurobloc in Europe

[b]NDO: Neurogenic detrusor overactivity, OAB: overactive bladder (See Chap. 8 of this book for more details on bladder function and indications)

than other toxins for associated neck pain and the higher doses of Myobloc are more effective than lower doses for this indication. [7, 8] It is used, off-label, for treatment of spasticity and muscle spasms as well as excessive drooling based on clinical trials demonstrating its efficacy. Myoboc is provided as a - ready to use - solution and does not require reconstruction (mixing the toxin with saline). The units of Myobloc are very different from the units of other botulinum toxins. Myobloc vials contain 2500, 5000 and 10,000 units. Each 40–50 units of myobloc approximates 1 unit of Botox or Xeomin and 2.5–3 units of Dysport.

Preparation/Injection

All botulinum toxins are administered through intramuscular or intradermal (into the skin) injection. Before injection, Botox. Xeomin and Dysport need to be prepared - the toxin which is provided as a white powder in a vial needs to be reconstituted with salt water (saline). For most indications, the dilution is with 1–2 cc of normal saline (0.9% sodium salt solution commonly used in clinical practice). When injecting large muscles, mostly for spasticity, many injectors use 4 or even 8 cc dilution to enhance the diffusion of the toxin within the muscle. After inserting sterile saline into the vial, in case of Botox, the vial is gently shaken 3–4 times to accelerate the mixing process. For Xeomin, it is recommended to invert the vial several times. For most indications, a 1 cc thin syringe with 10 divisions is used to draw the solution. Because of the small size of the syringe this is sometimes problematic. The drawing requires effort and often some of the solution is lost in the process. Adding a couple of cc's of air into the vial (with a 2–3 cc syringe) before drawing the solution into a 1 cc syringe will help. This will allow smooth drawing of the solution into the small syringe and full recovery of the solution from the vial.

For most indications of botulinum toxin therapy (with Botox or others), (injecting muscles and skin around the head), spasticity and dystonias (neck, limbs), injection are done with a small and thin needle to avoid pain and discomfort. A 27.5 gauge needle, ¾ inch long, is commonly used in clinical practice for these injections. For injections into the face in case of blepharospasm and hemifacial spasm as well as injecting into sweat gland and salivary glands a smaller needle, gauge 30 is preferable. For most indications, injections are performed quickly and do not need prior numbing of the skin. The exception is injections for excessive sweating (palm, sole of the foot, arm pit) which requires multiple injections (20–30 under the skin, gride- like). For this indication, the skin is usually numbed with an anaesthetic cream first (for example Emla cream), applied to the intended area, 1–2 h before injections. The skin is then cleaned and can be further be numbed by an anaesthetic spray during the injections.

Specific side effects after treatment for each medical indication are discussed in different chapters of this book. The safety issues with botulinum toxins, in general, and for specific indications are discussed in Chap. 15.

Non –FDA Approved Botulinum Toxins Used in Far East Asia

Prosigne

Prosigne is a type A toxin which was developed by Chinese scientists at the Lanzhou Institute. The toxin has properties similar to other type A toxins and targets the same set of proteins in nerve-muscle junction to prevent release of neurotransmitters from vesicles located inside the nerve terminal (see Chap. 1). The external expedients of Prosigne per vial, unlike all other type A toxins is porcine gelatin 5 mg,dextran 25 mg and sucrose 25 mg with a protein load of 4-5 ng/100 units [9]. It is generally believed that Prosigne's potency is close to that of Botox. In one report, a similar potency has been described (Botox/Prosigne 1:1 ratio) [9] while another report [9] used 1:1.5 ratio, with Botox being more potent. Although Prosigne has been shown to be effective in several indication similar to Botox as well as for some pain indications, it is not approved by FDA for use in the US.

Meditoxin/Noronox

Meditoxin (Noronox) is a type A toxin manufactured by Medytox company in South Korea; it is widely used in Asian countries. The toxin has almost an identical structure to Xeomin and possesses a very low protein load. Noronox comes in 100 unit vials with a potency similar to Botox. The external expedient in meditoxin is a plant protein unlike that of Botox which is serum albumin. A liquid formulation of Meditoxin has been developed which does not need reconstitution and can be kept at room temperature. In 2013, Allergan bought the license for liquid Meditoxin for potential future distribution in US.

Meditox has been studied recently in several high quality investigations for possible approval by FDA. A phase III study (see definition of study phase later in this chapter) was completed on 7–4-2017 for blepharospasm; blepharospasm is involuntary eyelid closure and spasms. Another phase III study was completed in 7–6-2017 for torticollis; torticollis is a medical condition characterized by involuntary neck movements and postures, often associated with neck pain . Another phase III study for wrinkles with Meditox was initiated on 4–17-2017.

Definition of Clinical Trials

Before a drug gets approved by FDA for human use, it needs to go through three phases of clinical trials. Phase I clinical trial investigates if the drug is safe for human use. This is done usually on a small number of patients (n = 10–30) assessing

the effect of different dosages of the drug and recording carefully tolerability and, side effects. It is not the test of efficacy of the drug, although some observations on the patients' response to the drug can be made. No placebo (sham drug) is involved in a phase I clinical trial.

In a phase II clinical trial, larger number of patients are tested (usually between 25–100) looking at the efficacy of the drug for a specific indication based on different doses that have been found to be safe in the phase I trial. The patients' response to the drug is carefully tested by using different rating scales. This is usually a blinded and placebo controlled study i.e. the effect of the drug is blindly compared with a placebo (usually salt water injection in case of botulinum toxin injection). Blinding means that the design of the study is as such that neither the patient nor the physician know the type of injection (toxin or placebo).

A phase III clinical trial is usually a multicenter trial involving a large number of patients in the hundreds or thousands. Phase III clinical trials use a placebo arm and the response of the patients' symptoms to the therapeutic agent (for instance botulinum toxin) is measured against a placebo. The results are presented after careful statistical assessment. Phase III clinical trials are longer than phase I and II, often lasting for months.

A phase IV clinical trial is done after FDA approval in order to investigate the clinical efficacy, quality of life and cost effectiveness in greater detail. These studies may involve several thousands of patients and are often conducted over several years.

The FDA approval for any drug (including botulinum toxins) for use in the US is based on availability of high quality, phase III trials. In most cases, FDA requires two phase III, class I (very high quality) studies that have proven the efficacy of the therapeutic agent for a given indication. For some indications, however, FDA has approved a drug for US use based on only one large, multicenter and exceptionally well done, Class I, phase III trial.

Study Class and Efficacy Evaluation

In this book, the definition of study class and efficacy are based on the criteria previously published by the American Academy of Neurology (AAN) [10, 11]. Clinical trials are classified into Class I, II, III and IV based on the quality of the study:

A class I study (highest quality) is a randomized, controlled clinical trial of the intervention of interest with masked or objective assessment in a representative population. The study is double blind i.e. the rating physician and the patient do not know what the given pill or injection was (drug or a placebo - a sham substance). Usually another physician not involved in the rating (assessment of symptom improvement) or a nurse conceals the information in a computer. Also, there should not be any substantial differences between the two study groups (toxin or placebo) in regard to relevant characteristics (sex, age, duration of illness, etc) .

The following also need to be clearly defined:

a. How the allocation to drug group versus placebo group is concealed from the patient or rating physician
b. Primary outcome(s)
c. Exclusion and inclusion criteria
d. Adequate accounting for dropouts- The dropout should not exceed 20% of the studied population

A class II study is a randomized, double blind study which lacks one of the 4 additional criteria (a–d) mentioned above or a prospective cohort which meets b,c,d citeria. A class III study is all other controlled trials (including well- defined natural history controls or patients serving as their own control) in a representative population where outcomes are independently assessed or independently derived by objective outcome measurements. Class IV studies are all other studies not meeting Class I, II and III criteria. These studies are often retrospective reviews of a small cohort.

Based on the availability of high quality studies, the efficacy of a drug has been classified as A, B, C and U. An A level of efficacy means that the efficacy is established or refuted based on two class I studies. For instance, the efficacy of Botox treatment is established in chronic migraine based on two class I studies (Chap. 4). A level B efficacy means probable efficacy (or lack of it) based on one class I or two class II studies. An example efficacy of Botulinum toxin in nerve damage due to diabetes (diabetic neuropathy) has been assigned a B level based on two class II studies (Chap. 5). Level C efficacy denotes possible efficacy or possible lack of efficacy based on one class II study (efficacy of Botox in female pelvic pain- one positive class II study). The U efficacy level means that the reported high quality studies (class I and II) have described contradictory results or there are no high quality studies reported for that indication. An example for that would be the use of botulinum toxin therapy in a condition called myofascial spasm. Throughout this book, wherever study class and efficacy level is quoted, it refers to the above described classes and levels defined in the American Academy of Neurology (AAN) guidelines.

References

1. Chen JJ, Dashtipour K. Abo-, inco-, ona-, and rima-botulinum toxins in clinical therapy: a primer. Pharmacotherapy. 2013;33:304–18.
2. Brin MF, Comella CL, Jankovic J, Lai F, Naumann M. CD-017 BoNTA study group. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. Mov Disord. 2008;23:1353–60.
3. Dressler D. Five-year experience with incobotulinumtoxinA (Xeomin(®)): the first botulinum toxin drug free of complexing proteins. Eur J Neurol. 2012;19:385–9.
4. Dressler D, Bigalke H. Long-term stability of reconstituted incobotulinumtoxinA: how can we reduce costs of botulinum toxin therapy? J Neural Transm (Vienna). 2017 Aug 2; https://doi.org/10.1007/s00702-017-1767-y. [Epub ahead of print]

5. Lorenc ZP, Kenkel JM, Fagien S, et al. A review of AbobotulinumtoxinA (Dysport). Aesthet Surg J. 2013;33(1 Suppl):13S–7S.
6. Lew MF, Chinnapongse R, Zhang Y, Corliss M. RimabotulinumtoxinB effects on pain associated with cervical dystonia: results of placebo and comparator-controlled studies. Int J Neurosci. 2010;120:298–300.
7. Kaji R, Shimizu H, Takase T, Osawa M, Yanagisawa N. A double-blind comparative study to evaluate the efficacy and safety of NerBloc® (rimabotulinumtoxinB) administered in a single dose to patients with cervical dystonia. Brain Nerve. 2013;65:203–11.
8. Quagliato EM, Carelli EF, Viana MA. A prospective, randomized, double-blind study comparing the efficacy and safety of type a botulinum toxins botox and prosigne in the treatment of cervical dystonia. Clin Neuropharmacol. 2010;33:22–6.
9. Rieder CR, Schestatsky P, Socal MP, et al. A double-blind, randomized, crossover study of prosigne versus botox in patients with blepharospasm and hemifacial spasm. Clin Neuropharmacol. 2007;30:39–42.
10. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008;71:1634–8.
11. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology. 2008;71:1639–43.

Chapter 4
The Role of Botulinum Toxins in Treatment of Headaches

Introduction

Headache is a common ailment. On average, 50% of the population experiences one headache per month and a quarter of population acknowledge having one headache per week. The international society for classification of headaches, categorizes headaches into primary and secondary headaches. Primary headaches are those that occur in individuals with no evidence of brain disease on brain imaging or laboratory testing, whereas secondary headaches arise as a result of brain pathology or systemic disorders. Although secondary headaches reflect a more serious condition (tumor, inflammation, bleeding, etc), primary headaches can be as severe and as disabling.

The major primary headache disorders consist of migraine, tension headaches and cluster headaches. Over the past 17 years, the effects of botulinum neurotoxin therapy on primary headaches has been studied extensively especially with onabotulinum toxin A (Botox) (see Chap. 3 for different types of botulinum toxins used). These studies, so far, have shown the efficacy of Botox in treatment of chronic migraine, an indication which received approval in summer of 2010 in Europe and Canada; it received approval by FDA for use in US, later that year.

Migraine and Chronic Migraine

The word migraine is derived from the French word of migraine (pronounced migren) which itself originates from the Greek word hemikrania (pain involving half of the head – Galen 200 AD). Although in many patients with migraine, pain of migraine involves mainly one side of the head, a sizeable number of migraine victims complain of bilateral headaches. Migraine is much more common among women than men with a reported prevalence of 17% among the former and 6%

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_4

among the latter [1]. The exact cause of this huge gender difference in migraine is not clear but, undoubtedly, hormonal issues play a major role as migraine frequency often diminishes during pregnancy and after menopause following the drop in estrogen levels. Migraine's impact on the quality of life is substantial. Migraine is currently rated as the seventh cause of medical disability [2]. Migraine headaches usually begin during the second and third decades of life and decrease substantially after age 40 [3]. Migraine is considered a genetic disease since over 50% of the patients report a family history of migraine.

The pathophysiology of migraine is still not fully understood. The old concept that a sequence of constrictions of brain vessels followed by dilatation causes migraine is no longer tenable. According to current thinking, before onset of pain, an electrical wave starts and travels over the cortex resulting in depression of brain activity and release of potassium, calcitonin gene related peptide (CGRP) and other substances. These substances lead to inflammation of brain coverings which then conveys signals to the pain sensitive trigeminal system inside and outside of the brain. This system innervates the skull, scalp and blood vessels; irritation and sensitization of this system results in pain. A genetically related mechanism triggers the initial event of this cascade in migraine which is yet to be explained.

Clinically, migraine headaches are often of moderate to severe intensity and on the average, last from 4 to 72 h. Attacks may be one sided, but changing sides is not unusual. During the attacks, patients often complain of nausea and report unusual sensitivity to light or sounds. Most patients prefer to go to a quiet room, close their eyes and avoid noisy environment.

In 20% of the patients, a migraine attack begins with an" aura ". Aura means "breeze" in Greek language and, in migraine denotes a transient objective sensation before the onset of headache. The most common type of aura in migraine is a visual aura. Patients describe seeing lights in part of their visual field. These light auras are usually on one side of the patients' visual fields (sometimes affecting half of the field in both eyes) while taking many shapes and forms. They can present in form of flickering or zigzag lights also called scintillations. These lights often start in a small part of the visual field and then evolve into larger areas. The enlarging lights in the field of vision (positive aura), sometimes end to momentary loss of vision in the same area (scotoma). In some patients, the scotomas or negative auras can occur without positive auras. Another common aura in migraine is a somatosensory aura which presents with experiencing unusual sensations over the face or parts of body. These sensations are usually in form of tingling, numbness or transient loss of sensation, affecting one side. Such experiences in older individuals need to be differentiated from initial symptoms of an impending stroke which is totally different from migraine. Other auras such as experiencing intense smell or taste or having episodes of vertigo are less common.

Patients may explain their first migraine as the most severe headache of their life with a very sudden onset. Such headaches (thunderclap headache) need to be investigated by computed tomography (CT scan) or magnetic resonance imaging (MRI) to ensure that they do not represent bleeding inside the head as a consequence of a

ruptured aneurism that requires immediate and urgent care due to its potentially life threatening nature (re-bleed).

Based on the frequency of headaches, migraine is classified as episodic or chronic migraine. The term episodic migraine defines a form of migraine with headache days of less than 15 per month while definition of chronic migraine requires 15 or more headache days per month, with at least 8 of 15 of them being of migraine type.

Treatment of migraine includes abortive and prophylactic (preventive) measures. Abortive medications suppress the acute pain, whereas prophylactic medications, prevent recurrence of severe headaches. Abortive treatments are short term and usually limited to the day of the migraine attack. Prophylactic treatments require taking daily medications. Migraine is an underdiagnosed disease and it is generally believed that preventive treatment in migraine is also underutilized.

Treatment of Acute Attacks

Three categories of medications are capable of inducing significant relief of acute migraine attacks within 2 h, usually in over 50% of the patients. These abortive drugs consist of Triptans, the Ergot derivative DHE and antiemetic (against vomiting) agents (metoclopramide, chlorpromazine). Triptans (sumatriptan, eletriptan and several others) are available in oral and injectable forms as well as nasal spray with the latter two being more useful in patients with nausea or vomiting. Subcutaneous injection of injection or nasal spray DHE have similar effects, while intravenous DHE combined with metochlopromide is often used for aborting severe attacks. For milder attacks, one can use over the counter drugs such as acetaminophen or aspirin. Transcranial magnetic stimulator is a FDA approved device that provides a magnetic pulse to the brain surface (through the skull) and has been shown to make 17% of the patients free from acute migraine headaches within 2 h [3].

Preventive Treatment

A large number of medications are now available for prevention of acute attacks. Among these medications the most commonly used are tricyclic antidepressants (amitryptiline and nortryptiline), betablockers (propranolol, nadolol, metoprolol, timolol), anticonvulsant agents (topiramate and divalproex sodium), and most recently, monolclonal antibodies targeting, CGRP (calcitonin gene related peptide). CGRP is a major pain transmitter and modulator that based on laboratory tests, plays a major role in the pathophysiology of migraine. In high quality, blinded, phase 3 studies (see definition in Chap. 3), this group of drugs has been found to be extremely effective in prevention of migraine [4]. The mode of treatment

application are subcutaneous or intravenous injections, used once every one to three months. Monoclonal antibody treatment is about to be approved by FDA for use in the US.

Unfortunately, all medications used for prevention of acute migraine attacks have a low to medium rate of efficacy especially in chronic migraine when the attacks occur 15 or more days per month. Moreover, the side effects of these medications such as hypotension (low blood pressure) and sexual dysfunction (beta-blockers), unusual sensory experiences, cognitive decline, depression, weight loss (topiramate), tremor and hair loss (divalproex), dry mouth, urinary retention and weight gain (tricyclic antidepressant and divalproex) concerns many patients. Over the counter medications such as co-enzyme Q, magnesium, vitamin B1 and melatonin or acupuncture have questionable preventive effect. Exercise, yoga, and meditation help some patients through relaxation. Furthermore, drugs that are used for aborting the acute migraine attacks, are themselves, sometimes hard to tolerate due to undesirable side effects. For instance, triptans and DHE are contraindicated in coronary artery disease and can cause dizziness, nausea and light headedness, while antiemetic medications cause sedation and acute abnormal movements (dystonia: twisting of the limbs and akathisia: excessive restlessness). For these reasons a mode of preventive treatment which is effective and has a low side effect profile remains desirable for prevention of frequent migraine attacks [1].

Botulinum Toxin Treatment of Migraine

During 1980's and 1990's animal studies demonstrated that onabotulinumtoxinA (Botox) can block the release of pain modulators and pain transmitters from nerve-muscle junction [5]. This made researchers think that Botox injections into muscles around the head, by influencing the pain transmitters, may help patients with headaches. During 1990's several reports indicated that Botox injection into forehead muscles can improve forehead wrinkles. To the surprise of clinicians, some migraine patients who received Botox into forehead for cosmetic purposes reported reduction of intensity and frequency of their headaches. Following these observations, a headache specialist, Stephen Silberstein and his co-workers conducted the first randomized, double blind, placebo controlled clinical trial (see Chap. 2 for definition of clinical trial) of Botox in patients with migraine [6]. In that study, 123 patients with migraine were stratified into three groups receiving either Botox 75 units, Botox 25 units or placebo (normal saline) into the forehead muscles. Although the study did not show a statistically significant improvement of the primary outcome measure – increased pain free days/month, it showed that injection of Botox into forehead muscles reduces the intensity of migraine attacks and the number of pain days/month. It took another 10 years before the role of Botox in treatment of migraine was established. During these 10 years, several studies with Botox in episodic migraine (with pain frequency of <15/month) failed to show any efficacy. However, in 2010 publication of PREEMPT studies demonstrated that injection of Botox into

the pericranial (around the head) muscles with certain injection paradigm and dose can significantly reduce the number of pain days in patients with chronic migraine. The total dose and number of injected sites in PREEMPT studies was substantially higher than that of prior studies.

PREEMPT Studies

The two PREEMPT studies were multi-center and investigated the efficacy of Botox in chronic migraine (15 or more pain days per month), on a total of 1384 patients. PREEMPT studies were double blind, meaning that the patients did not know what they were receiving; physicians and raters of the response were also blinded to the type of the injections. Both studies also had a follow up, open label (unblinded arm). The blinded arm of the studies lasted for 24 weeks with placebo or Botox injection every 12 weeks. Patients were evaluated with weekly visits during which they had several ratings of pain, sleep, and quality of life throughout the duration of the study. The open, unblinded arm which began after completion of the blinded arm, lasted 32 weeks during which the patients received Botox only and were evaluated the same way for response. Evaluation of the pooled data from the two PREEMPT studies showed that a single injection of Botox produced not only reduction of pain days and migraine episodes per month but also reduced the pain intensity within each episode [7]. All findings had a high level of statistical significance ($P < 0.0001$). Since then, Botox has been used for treatment of chronic migraine on thousands of patients. The positive results of PREEMPT studies raised several practical questions:

- Can the positive effect of Botox treatment in chronic migraine be sustained over a long period of time (years) with repeat injections?
- A sizeable number of patients with chronic migraine also have superimposed medication overuse headaches i.e. they have a second pain issue. Does this population of patients with chronic migraine also respond to Botox therapy?
- Generally, patients with chronic migraine have a poor quality of life. Do the positive effects of Botox therapy in chronic migraine lead to improvement of quality of life?
- Is long term- treatment of chronic migraine with Botox safe? Are there any serious side effects with long-term use?

Aurora and co-workers [8], studied the sustenance of Botox effect on 1005 patients with chronic migraine who received Botox injections into pericranial (around the head) muscles after 5 cycles of treatment (every 3 months). Patients continued to enjoy pain relief during all five cycles of treatment (56 weeks) and also showed a substantial improvement in their quality of life as measured by migraine-specific quality of life questionnaire scores. Another group of investigators demonstrated that quality of life improved significantly in both in blinded and open label phase of the PREEMPT study in the Botox group (607 patients) compared to the

placebo group (629 patients) [9]. Silberstein and co-workers [10], studied another cohort of PREEMPT population. Of 688 patients who received Botox, 49.3% demonstrated 50% or more reduction in the frequency of headache days after first injection with additional 11% and 10% first time responders observed during the second and third cycle of injections. In another study which focused on patients with migraine and medication overuse headaches [11], treatment with Botox decreased the frequency of headache and migraine days, headache intensity, number of severe headache days and percentage of patients with severe HIT-6 scores (poor quality of life). The authors concluded that Botox treatment is effective in patients with chronic migraine and medication overuse.

In recent years, a number of authors have investigated the utility of Botox therapy in migraine outside clinical trials and in real- life situations. These studies [12, 13], have confirmed the positive results of clinical trials of Botox therapy in chronic migraine. A recent, large survey conducted in 28 Italian health centers also concurred with the conclusion of these real-life studies [14].

Sites of Botox Injection, Recommended Dose Per Site and Per Session

The most common injection technique currently used for treatment of chronic migraine is the one used in the PREEMPT studies [15]. The PREEMPT protocol recommends injecting 5 pericranial (around the head) muscles consisting of three forehead muscles (corrugator, procerus, and frontalis), one muscle at the temple (temporalis) and one muscle at the back of the head (occipitalis). Two other injection locations are into the upper neck and shoulder muscles (splenius and trapezius muscles) (Fig. 4.1). The function of these muscles and the number of injections per muscle and does per injection sites are presented in Table 4.1. The total dose per session is 165 units with an option to increase it to 195 units, per the discretion of the injecting physician.

In practice, patients often express concern about the number of injections, thirty one, recommended by the PREEMPT group. Jabbari and co-workers at Yale have demonstrated that similar results can be achieved with a different injection paradigm that includes only 21 injection sites (Fig. 4.2) . In this injection scheme, injection sites at the temples are reduced to two on each side (using a larger dose of 15 units per site) and occipital injections to one on each side (5 units). Three injections, each 10 units are given into the posterior neck muscle (splenius), on each side. The six trapezius injection sites that are recommended by PREEMPT group, are eliminated from this paradigm [16]. Although some authors expressed concern that injection of higher doses into the neck may cause muscle weakness, the Yale group did not notice any weakness of neck or temporalis muscle after thousands of Botox injection sessions performed for treatment of chronic migraine. The total dose per session is 175–200 units, comparable with that of PREEMPT (165–195).

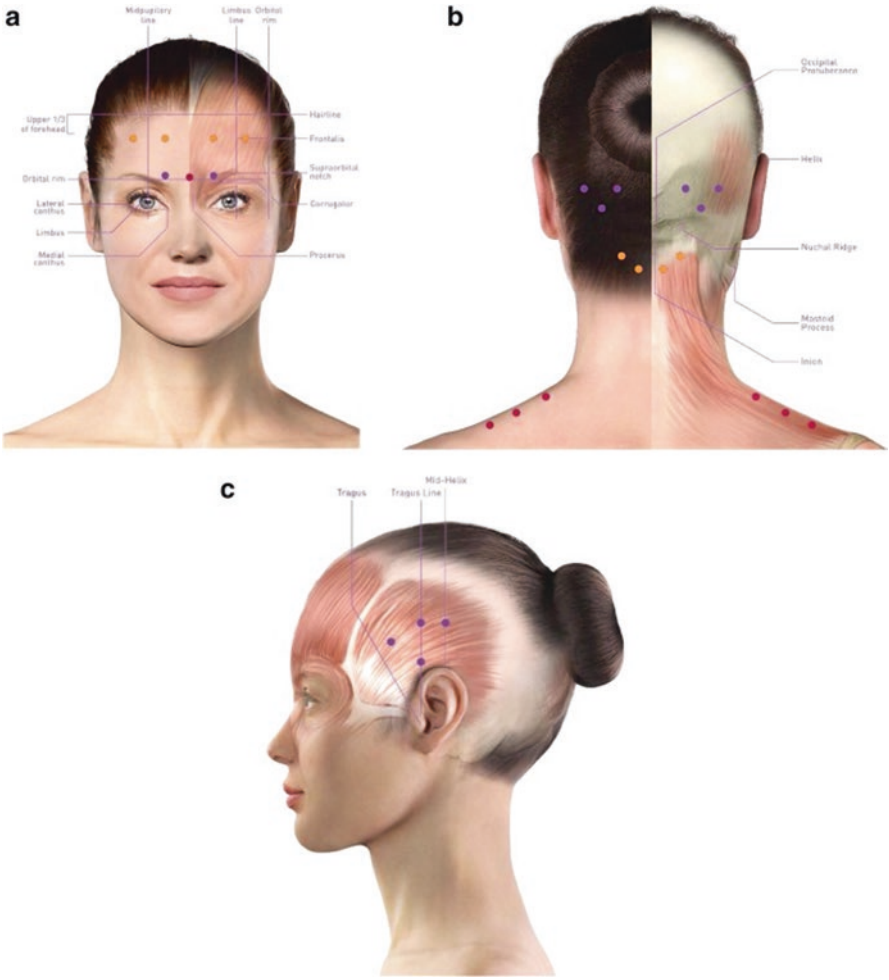

Fig. 4.1 Sites of Botox injections for treatment of chronic migraine as recommended by the PREEMPT Study group. From Blumenfeld et al. 2017 [15]. In Headaches. With permission from the Publisher, Wiley & Sons

How to Inject?

Botox comes in small vials with the active powdered ingredient sitting at the bottom of the vial. Botox has to be diluted with normal saline before injection. Some injectors like to add 1 cc and some add 2 cc of normal saline into the Botox vial containing 100 units of the toxin. This author prefers 1 cc dilution which allows injecting smaller volumes per site. After adding saline into the Botox vial, the solution is shaken gently and then is drawn into a small, thin 1 cc syringe with 10 divisions each representing 0.1 cc. When using 1 cc dilution, each 0.1 cc division of the

Table 4.1 Injection paradigm recommended by the PREEMPT study: injected muscles, muscle location, muscle function and the dose of Botox administered per site(s)

Muscle	Location	Function of muscle	Number of injection sites per muscle	Dose per injected site
Corrugator	Above the medial edge of eyebrow	Draws the eye brows together and downward	One on each side	5 units x 2
Procerus	Helps to pull the skin between eyebrows downward	Pulling eyebrows together	Single muscle One injection at midline	5 units x 1
Frontalis	Whole forehead	Pulling eyebrows up	Two on each side, total 4	5 units x 4
Temporal	Temple	Closes the mouth	Four on each side, total 8	5 units x8
Occipitalis	Back of the head	Moves the scalp back	Three on each side, total 6	5 units x 6
Splenius	Upper neck	Turns and tilts the head to the same side	Two on each side, total 4	5 units x 4
Trapezius	Shoulder	Moves the shoulders up	Three on each side	5 units x 6

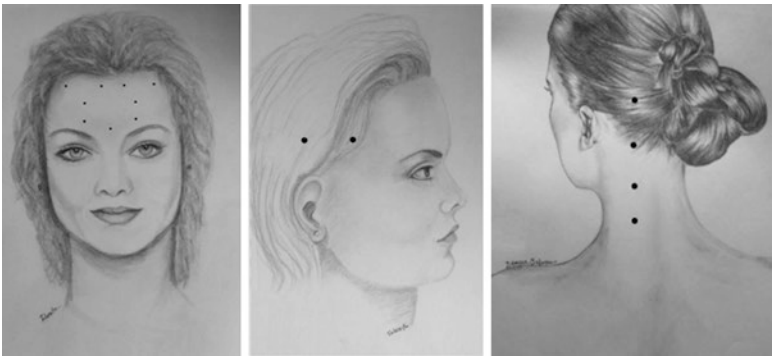

Fig. 4.2 The site of injections in the method used by Yale group for treatment of chronic migraine [16]. Drawings courtesy of Tahereh Mousavi M.D. and Damoun Safarpour M.D.

syringe will contain 10 units of Botox. Botox injections into the skin and muscles for migraine are superficial and performed with a small and thin needle (¾ inch, 27.7 or gauge 30 needle). In experienced hands, injections into pericranial sites, upper neck and shoulder muscles cause minor discomfort. Usually there is no bleeding, but when there is some bleeding, it stops quickly when wiped by a dry gauze. The injections can be done with the patient lying down or sitting up. This author prefers injecting migraine patients in the sitting up position. The whole procedure takes approximately 15 min.

Accuracy of dilution is very important in botulinum toxin therapy. This is particularly true when treating migraine patients since several muscles are small, hence, inaccurate dilution lead to overdosing and unpleasant side effects. For instance, small corrugator and procerus muscles are too close to the eye (see Figs. 4.1 and 4.2), and wrong dilution can lead to weakening of small muscles around the eye causing drooping of the eye lid or double vision. If the Botox solution is prepared and dilution is done by someone other than the injecting physician, it is the responsibility of the injecting physician to double check the accuracy of the dilution before injecting the patient.

Side Effects of Botox Therapy in Chronic Migraine

Side effects that develop following Botox treatment of migraine are minor and transient. In the large PREEMPT study consisting of 1384 patients, temporary pain at the site of injection, minor local bleedings (when the tip of the needle nicks a small blood vessel), mild muscle weakness and eyelid drooping occurred in 2–6% of the patients [8] Drooping of the upper eye lid can last for several weeks, but in my experience, can be easily avoided by careful placement of the thin needle into the lower forehead muscles (procerus and corrugator -see Figs. 4.1 and 4.2), away from the upper eye lid. PREEMPT authors reported no serious side effects, safety and tolerability issues that concurred with the experience of clinicians in the real-life situations.

Several studies have compared the preventive effect of Botox therapy in chronic migraine with the effect of two major headache preventive drugs, topiramate and divalproex. Side effects were more common in topiramate and divalproex groups. More patients in topiramate and divalproex groups discontinued treatment due to undesirable side effects than the group that received Botox (24% versus 7% and 27% versus 3% for topiramate versus Botox and Divalproex versus Botox, respectively) [17, 18].

Episodic Migraine

The term episodic migraine defines headaches with a frequency of less than 15 times per month. Seven high quality, blinded Class I and II studies (see Chap. 3 for definition of study class) assessed the efficacy of botulinum toxin therapy in episodic migraine. Three of the seven studies have used similar or higher doses than PREEMPT studies. All studies failed to show efficacy of botulinum toxin treatment in episodic migraine. In one study, however, investigation of a subset of the studied cohort, showed that Botox treatment, significantly reduces the intensity and frequency of headaches in patients with 12–14 headaches per month but not among

those with less than 12 headache days per month. In 2016, the Development Guideline Subcommittee of the American Academy of Neurology(AAN), based on the above data, reported Botulinum toxin treatment as ineffective in management of episodic migraine [19].

Tension–Type Headaches

Tension Headaches are the most common type of headaches with a prevalence of 38% in the US population [20]. Compared to migraine, tension headaches are more often bilateral and associated with scalp tenderness and less often associated with nausea and vomiting. Also, most tension headaches are less severe than migraine. The prevalence of chronic tension headaches (15 or more headaches per month) is similar to that of chronic migraine it is 2% in the general population [21]. Six high quality clinical trials (class I and II), two with Botox and four with Dysport (both type A toxins), assessed the efficacy of botulinum toxin A in tension headaches, but none showed efficacy. A meta-analysis study (see Chap. 3 for definition) of the reported data on tension-type headaches, published in 2012, also found botulinum toxin treatment ineffective in tension-type headaches [22]. A close scrutiny of these studies, however, demonstrates that the doses and number of injections in these studies was less than that of PREEPT investigation that had proved efficacy of Botox in management of chronic migraine. The most recent report from the Guideline Development Subcommittee of AAN defines botulinum toxin therapy in TTH as "probably ineffective." [19]

Secondary Headaches

The efficacy of botulinum toxin treatment has been rarely studied in patients with secondary headaches. Approximately 20% of patients suffer from recurrent headaches after head trauma. Although no controlled and blinded studies have been reported on the efficacy of botulinum toxin treatment in patients with post-traumatic headaches, some preliminary, open label (unblinded) observations suggest that Botox may help some of these patients. Yerry and co-workers [23], evaluated the results of Botox injection into the pericranial (around the head) muscles in 64 war veterans with head injury. Most patients had blast injury and 63 of them were male. Botox was injected according to the PREEMPT protocol for chronic migraine. Forty one patients (64%), reported improvement of their headaches.

Economic Issues

Several recent studies have shown that Botox treatment of chronic migraine (despite high cost of Botox) is economically sound and advantageous to the patients. In a recent study of 230 patients with chronic migraine [24], treatment with Botox over the six- month period resulted in 55% and 57% reduction in emergency department visits and hospitalizations, respectively. The investigators reported a cost reduction (saving) of $1219 per patient over the six- month period of Botox treatment. More recently, Hepp and co-workers [25], have assessed headache-related health care utilization at 6, 9 and 12 months in a group of chronic migraine patients treated with Botox and compared it with another group treated with oral migraine prophylactic medications (OMPM). Using a regression analysis method (a form of statistical method), they found that the group that received Botox had 20%, 21%,19% less emergency department visits over 6, 9 and 12 months and also 47%, 48%, 56% less hospitalizations compared to the OMPM group, respectively.

Conclusion

In 2010, after approval of Botox in Europe, Canada and US, a new era was reached in the medical management of chronic migraine. In many patients, Botox treatment eliminated the need for additional daily oral medications or led to the reduction of existing medications. Long-term follow up of patients with chronic migraine has shown that efficacy of Botox continues over years of treatment and actually improves after the second and third injection sessions. Comparative studies have demonstrated that Botox has less side effects compared to major preventive medications for migraine and fewer patients discontinue Botox treatment compared to those who take oral preventive medications. One treatment session every 3–4 months versus taking daily oral medications is another advantage of Botox therapy for management of chronic migraine. Over the long run, despite its expense, treatment of chronic migraine with Botox has proven economically feasible due the reduction of expensive emergency department visits and hospitalizations. To date, all high quality studies (Class I and II) of botulinum toxin therapy in chronic migraine have been conducted with Botox. Additional studies are needed to assess the efficacy of other types of botulinum toxin A (for example Xeomin or Dysport) and the botulinum toxin B (Myobloc) in management of chronic migraine.

References

1. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68:343–9.
2. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries,

1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1545–602.
3. Charles A. Migraine. NEGM. 2017;377:553–61.
4. Tso AR, Gadsby PG. Anti-CGRP antibodies: the next era of migraine prevention? Curr Treat Options Neurol. 2017, Aug;19(8):27. https://doi.org/10.1007/s11940-0463-4.
5. Jabbari B. Chapter 2. In: Jabbari B, editor. Botulinum toxin treatment of pain disorders. New York: Springer; 2015. p. 15–25.
6. Silberstein S, Mathew N, Saper J, Jemkins S. Botulinum toxin type A as migraine preventive treatment. For the Botox migraine clinical research group. Headache. 2000;4:445–50.
7. Dodick DW, Turkel CC, RE DG, et al. OnabotulinumtoxinA for treatment of chronic migraine:pooled results from the double blind, randomized, placebo controlled phases of PREEMPT clinical program. Headache. 2010;50:921–36.
8. Aurora SK, Dodick DW, Diener HC, et al. OnabotulinumtoxinA for chronic migraine: efficacy, safety and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Acta Neurol Scand. 2014;129:61–70.
9. Lipton RB, Rosen NL, Ailani J, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: pooled results of the PREEMPT randomized clinical trial program. Cephalalgia. 2016;36:899–908.
10. Silberstein SD, Dodick DW, Aurora SK, et al. Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. J Neurol Neurosurg Psychiatrry. 2015;86:996–1001.
11. Silberstein SD, Blumenfeld AM, Cady RK, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-weel pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013;331:48–56.
12. Khalil M, Zafar HW, Quarshie V, Ahmed F. Prospective analysis of the use of onabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, U.K. J Headache Pain. 2014;15:54.
13. Kollewe K, Escher CM, Wulff DU, et al. Long-term treatment of chronic migraine with OnabotulinumtoxinA: efficacy, quality of life and tolerability in a real-life setting. J Neural Transm (Vienna). 2016;123:533–40.
14. Tassorelli C, Aguggia M, De Tommaso M, et al. Onabotulinumtoxin A for the management of chronic migraine in current clinical practice: results of a survey of sixty-three Italian headache centers. J Headache Pain. 2017;18:66.
15. Blumenfeld AM, Silberstein SD, Dodick DM, et al. Insights into the functional anatomy behind the PREEMPT injection program: guidance on achieving optimum outcomes. Headache. 2017;57:766–77.
16. Schaefer SM, Gottschalk CH, Jabbari B. Treatment of chronic migraine with focus on botulinum neurotoxins. Toxins (Basel). 2015;7:2615–28.
17. Cady RK, Schreiber CP, Porter JA, et al. A multi-center doube -blind pilot comparison of onabotulinumtoxina and topiramate for the prophylactic treatment of chronic migraine. Headache. 2011;51:21–32.
18. Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type a and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache. 2008;48:210–20.
19. Simpson DM, Hallett M, Ashman EJ, Comella CL, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86:1818–26.
20. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. JAMA. 1998;270:3881–383.
21. Freitag F. Managing and treating tension -type headache. Med Clin North Am. 2013;97:281–92.
22. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA. 2012;307:1736–45.

23. Yerry JA, Kuehn D, Finkel AG. Onabotulinum toxin a for the treatment of headache in service members with a history of mild traumatic brain injury: a cohort study. Headache. 2015;55:395–406.
24. Rothrock JF, Bloudek LM, Houle TT et al. Real-world economic impact of onabotulinumtoxinA in patients wth chronic migraine. Headache. 2014;54(10):1565–73.
25. Hepp Z, Rosen NL, Gillard PG et al. Comparative effectiveness of onabotulinumtoxinA versus oral migraine prophylactic medications on headache-related resource utilization in the management of chronic migraine: Retrospective analysis of a US-based insurance data base. Cephalalgia. 2016;36(9);862–74.

Chapter 5
Neurotoxins in Management of Pain Disorders- New Encouraging Data

Intoduction

Pain is the most common human medical complaint. In most patients, pain is generated from a noxious stimulus which irritates the skin and peripheral nerves (peripheral pain). Cenral pain is uncommon. Less than 10% of pain experienced by the general population, is generated from a disease or disorder of the central nervous system (spinal cord or brain), in conditions such as stroke or multiple sclerosis (central pain).

In this chapter, we will briefly discuss the anatomy of pain pathways and the biologic and chemical substances which are essential in initiation and maintenance of pain. This will be followed by a brief description of animal studies that have shown how botulinum toxins can reduce pain by inhibiting pain transmitters and modulators. Finally, this chapter is predominantly devoted to discussion of the role and potential of botulinum toxin therapy in different human pain syndromes.

Anatomy of Pain Pathways

The nerves in the body are of two major types, motor or sensory. A third type, autonomic nerves which consists of very thin fibers, deal with the function of the viscera and glands. Sensory nerves convey sensations, including pain to the brain. Perception of pain requires a cascade of events which includes four phases; transduction, transmission, modulation and perception:

Transduction In this first phase of pain pathway, a noxious peripheral stimulus (thermal, mechanical, chemical) stimulates the peripheral sensory nerve endings which are scattered in the skin, muscle and joints. Located on these sensory nerve endings, are small receptors capable of sensing various types of the peripheral

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_5

stimulation (heat, pressure, chemical). These receptors which are called nociceptive (related to pain) receptors are also present on the body of the central sensory nerve cells (neurons) in the spinal cord. The pain which arises from damage to the tissue (skin, muscle, joint) is called nociceptive pain whereas the term neuropathic pain is applied to pain arising from damage to a peripheral nerve or the sensory pathways in the central nervous system.

Noxious stimulation of sensory nerve endings causes local secretion of several chemicals from the nerve endings which elicit stimulation of specific pain receptors. Furthermore, local tissue inflammation caused by accumulation of these chemicals leads to more stimulation of the nerve endings resulting in peripheral sensitization. Some of these chemicals such as histamine, bradykinin, Substance P are well known; several others are currently being studied.

Transmission During this phase, electrical activity that is generated from stimulation of the receptors travels along the sensory nerve. Sensory nerve fibers have different sizes. The fibers that convey the pain modality are thin (A- delta fiber) or very thin (C fibers). A- delta fibers conduct faster and are responsible for the short lasting and very sharp initial pain felt after exposure to a noxious stimulus. Slow conducting, C fibers produce the less intense, but longer lasting, pain that follows the initial sharp pain (Fig. 5.1- lower right).

On the path of the sensory pain fibers from periphery to the cortex (where the pain is perceived by cortical cells), there are three distinct sensory stations (Fig. 5.1). Each sensory station contains nerve cells that receive sensory fibers from the periphery and project their own sensory fibers more centrally to the next station and toward the cortex. The first sensory station is located in the dorsal nerve root close to the spine and is called dorsal root ganglion or DRG (Fig. 5.1-lower right).

The cells of DRG have a T shaped structure with a peripheral and central sensory fiber(axon). The peripheral axon of DRG receives sensory information (including pain) from the nerve ending via the previously described phenomenon of transduction. The central axon of nerve cell in DRG, enters the spinal cord, and connects (synapse) with the second sensory neuron in the dorsal part of the spinal cord (Fig. 5.1). The axon of this spinal sensory neuron crosses the cord and travels in the opposite side up to the lower part of the brain (medulla and mid-brain) (Fig. 5.1) where it gives collateral branches to a network of cells (reticular formation), involved in pain modulation (colored blue in Fig. 5.1). Higher, deep in the brain the sensory information from spinal nerve cells arrives in the third sensory station, named thalamus (Fig. 5.1). The sensory cells of the thalamus are in direct contact with the sensory cells of the cortex. There are several chemical agents which are involved in pain transmission through DRG to the central nervous system at spinal cord, thalamus and cortex levels. The two best known of these agents are glutamate and calcitonin gene-related peptide (CGRP). Noreadrenaline and serotonin are involved in pain modulation (Fig. 5.1- right side).

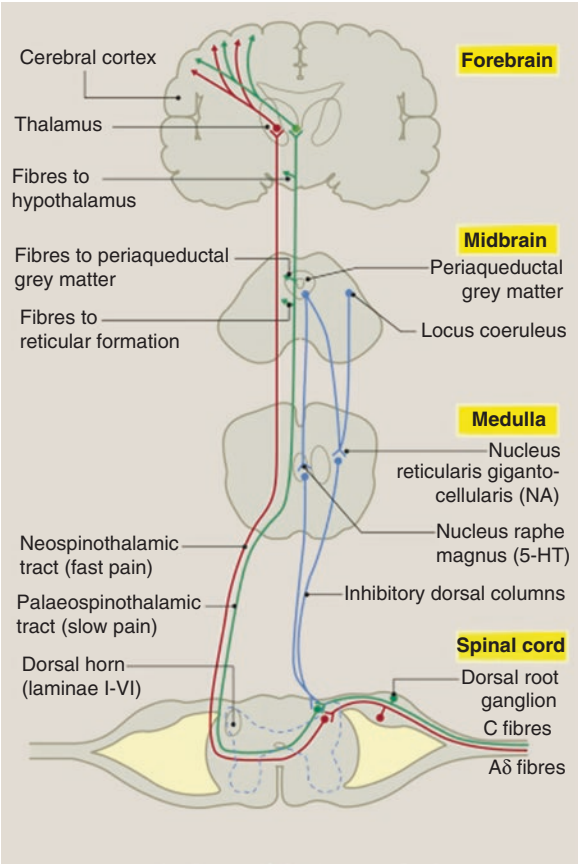

Fig. 5.1 Pain pathways. From Steeds Anatomy and Physiology of pain, Surgery (Oxford) 2016- Reprinted with permission from Elsevier

Pain Modulation

Human cortex exerts some control over the incoming pain volleys to the cortex. This is done through a descending sensory system which originates from the cortex and makes multiple synapses(contacts) with the nerve cells scattered in the medulla and midbrain within a netlike structure called reticular formation (Fig. 5.1). These cells receive collateral connections from the ascending sensory fibers as they travel within medulla and mid-brain toward the cortex. This modulatory effect is probably a safety mechanism which protects the cortex from excessive stimulation.

Pain Perception

The pain signals which reach the thalamus from the periphery reach three areas of the cerebral cortex (a layer of cells that cover the brain): the somatosensory cortex which is located in the parietal lobe and localizes the physical sensations including

pain, the limbic system consisting of a group of cells located in the medial aspect of the temporal and the frontal lobes dealing with the emotional aspect of painful stimuli and the frontal cortex that processes meaning and cognition of nociception (pain). The perception of pain therefore involves multiple cortical structures which combine sensation, emotion and conscious thought.

Animal Studies of Botulinum Toxins in the Field of Pain

Over the past 30 years, a large number of animal studies have shown that injection of botulinum toxins to animals can inhibit secretion of pain transmitters and prevent or reduce the pain behavior. Although most of these studies have been performed with onabotulinumtoxinA (Botox), studies with other type A toxins and with the type B toxin is also forthcoming (see Chaps. 2 and 3 for definition of different botulinum toxins). These studies have demonstrated that botulinum toxins can affect pain transmission via their influence upon nerve endings, dorsal root ganglia (DRG) and spinal cord sensory neurons.

Nerve Endings and Peripheral Receptors

In formalin model of pain, injection of formalin into the rat's paw causes sever sharp pain which lasts for seconds and then a less severe pain that last longer, minutes to hours. The first peak of this pain is due to the acute irritation of nerve endings by formalin whereas the second pain represents the irritating effect of local inflammation caused by formalin injection. Examination of the injected tissue (rat's paw) shows local accumulation of glutamate, a known pain transmitter and local presence of inflammatory cells. Injection of botulinum toxin type A (Botox) and type B toxin (Myobloc), 5 days before formalin injection, markely reduces the inflammatory peak of pain (second peak) and lowers accumulation of glutamate in the injected tissue [1, 2].

Dorsal Root Ganglion

Dorsal root ganglia, the first sensory nerve cell (neuron) which receives pain signals from the periphery when cultured, secrets substance P, a pain transmitter. Adding Botox to this culture inhibits the release of substance P from DRG cultures [3]. Moreover, recent data have shown that botulinum toxins reduce the expression of several newly discovered pain receptors on the nociceptive sensory nerve cells of spinal cord.

Spinal Cord Sensory Neurons

After intramuscular injection, the receptor protein that receives Botox at nerve-muscle junction (SNAP 25, See Chap. 1) travels to the spinal cord and influences the spinal sensory nerve cells (second sensory neurons which receive pain signals) [4].

Injection of botulinum toxin B into the paw of the rat reduces release of substance P (a chemical pain transmitter) from the spinal neurons after formalin activation [5].

Human Pain Syndromes

Botulinum toxins have shown efficacy after intramuscular or subcutaneous (under skin) injection in a variety of human pain syndromes. In this section, we will describe those pain syndromes in which research from high quality studies has provided compelling evidence for their efficacy.

Chronic Low Back Pain

Chronic low back pain is defined as a low back pain that lasts more than 12 weeks. Between 2–7% of patients with acute low back pain develop chronic low back pain. Low back pain is the leading cause of disability and a major burden to US and European economy. A multitude of disease conditions can cause low back pain, most notable among them, are chronic disc disease, narrowing (stenosis) of the spinal canal and arthritis of the spine. Management of chronic low back pain is a major medical challenge. Relief from medications is often partial, and side effects of strong pain killers and opioid compounds often interrupts the medical management.

There is evidence from blinded and high quality studies [6, 7], that injection of botulinum toxins into muscles close to the spine can relieve low back pain in at least 50% of patients with no history of prior surgery. The effective technique, developed by this author, advocates injection of Botox into the extensor muscle of the spine. Extension of the spine results from the function of three long muscles which originate from the base of the neck, join together at upper lumbar region to make a single bulk that ends at the lowest part of the spine and the pelvic bone. Five injections into the extensor muscles, one at each lumbar level (L1 to L5) is recommended. Injections are easy and quick and are done into the extensors of the spine, the most superficial muscle covering the spine. The injections need to be conducted under electromyographic guidance (a technique that monitors the electrical activity of the muscle) to ensure insertion of the needle in the proper muscle.

Using this technique, Jabbari and co-workers have investigated the effect of two type A (see Chap. 1 for definition of toxin types) botulinum toxins (Botox and Xeomin) on patients with chronic low back pain. The first study was conducted with Botox on 27 patients at Walter Reed Army Medical Center in Washington DC[6]. The second study was performed 10 years later at Yale University, using identical technique and dose on 33 patients with Xeomin [7]. The units of Botox and Xeomin are roughly comparable. The dose used in both studies was 40 units per level, for a total of 200 units for unilateral injection (in patients who had pain on one side) and 400 units for bilateral injection. The results of the two studies were almost identical showing that 52 to 54% of the patients with chronic low back pain experienced pain relief while a majority of the patients also reported improvement of their quality of life. Patients did not experience any significant side effects (weakness of the back or legs) in either of the two studies. A few patients (5%) developed a transient, mild flu like syndrome lasting a few days which is expected to happen in small percentage of patients after botulinum toxin therapy.

Other investigators who used different techniques, injected different back muscles and used different doses of Botox, failed to achieve improvement of low back pain. Since many different factors can cause low back pain, future studies will hopefully focus on studying individual subsets of low back pain to find which kind of low back pain (disc, arthritis, stenosis, strain, etc) responds best to botulinum toxin therapy. Using the efficacy criteria of the Guidance Development Subcommittee of the American academy of Neurology (See Chap. 2), the efficacy level of the type A toxin treatment (Botox and Xeomin) in chronic low back pain is B (medium efficacy, probably effective) based on two class II studies (see Chap. 2 for definition of study class) studies.

Patient Observation

A 65 year-old man who had experienced low back pain for several years was referred to Yale Botulinum toxin clinic for evaluation. There was no history of back injury and no surgical intervention. The pain affected the low back in the mid-lumbar region with no radiation to the lower limbs. A magnetic resonance imaging of the back showed diffuse degenerative spine disease but no acute pathology. Treatment with a large number of pain killers had not been helpful. The patient's examination was normal except slightly increased muscle tone in the low back area. Since the pain was predominatly on the right side, the patient was injected on the right side only (Fig. 5.2). The injection was into the extensors of the spine (erector spinae muscles) and was performed at five lumbar levels. The dose of Botox was 40 units per injection site for a total of 200 units. After a week, patient reported significant improvement of his low back pain. Over a 3 year period of follow up, he received Botox injections every 3–4 months and each time reported satisfaction with the therapy. He experienced no side effects.

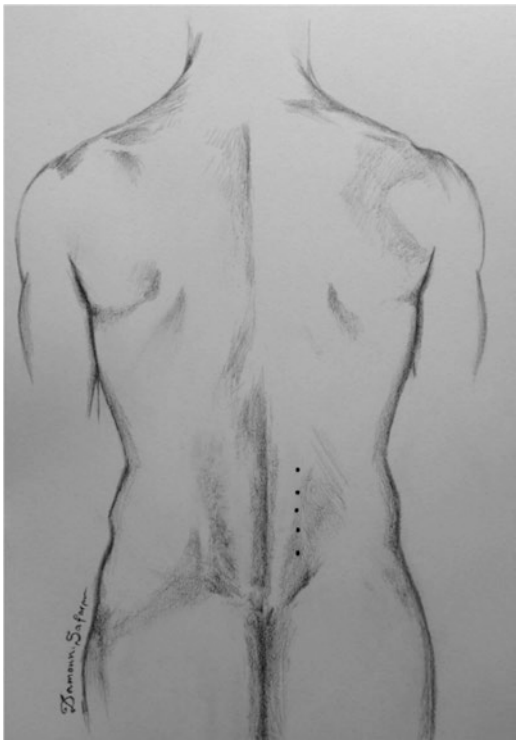

Fig. 5.2 The sites of injections on the reported patient treated for chronic low back pain. Drawing, coustesy of Damoun Safarpour M.D.

Pain After Shingles (Post–Herpetic Neuralgia–PHN))

Shingles (Herpes Zoster) results from reactivation of childhood chicken pox virus in the later years of life. The disease starts with eruption of small vesicles over the skin with a typical distribution pattern along the course of the nerve routes or peripheral nerves. Face, trunk or limbs may be involved. In the early stage, itch is the most disturbing complaint. After a few weeks, the vesicles dry up and leave scars and cause skin discoloration. Some patients with shingles may develop pain (post-herpetic neuralgia) during or shortly after healing of skin lesions. The pain is often described as severe, sharp and jabbing and is felt in the distribution of the involved nerves. When on the trunk, large parts of the body may be involved. The percentage of patients who develop pain after shingles, is highly dependent on the age at the onset of their symptoms; it is 5% among individuals younger than 60 and 20% among patients who are 80 years of age or older [8]. Vaccination against shingles in adults reduces the incidence of post-herpetic neuralgia. Pain of shingles may last for months or even years and can severely incapacitate the affected patient.

Treatment

Medical treatment of shingles consists mainly of administration of pain killers (analgesics). These include commonly used over the counter drugs such as aspirin or acetaminophen or the types of pain killers that specifically promote pain inhibition in the central nervous system by enhancing the effects of powerful inhibitory neurotransmitter GABA (Gaba aminobutyric acid), abundantly present at the junction of nerve cells (synapse). The major drugs in this category are carbamazepine (Tegretol), pregabalin (Lyrica) and baclofen (Liorisal). In more severe cases, a course of steroid therapy with prednisone may reduce the pain intensity. Inducing nerve block by injection of anaesthetic medications into sensitive skin regions, electrical stimulation of skin nerves or even spinal cord has been employed for management of recalcitrant pain after shingles. Unfortunately, despite these medical measures, a sizeable proportion of patients with shingles, continue experiencing disabling pain and live with impaired (often severely) quality of life. In some cases of shingles, poor response to pain treatment may be a reflection of extensive pathology distribution of the disease. It has been shown that shingle's pathology may not be limited to nerve damage or inflammation of the skin. The inflammatory cells may involve the spinal cord and can be associated with the presence of inflammatory cells in the cerebrospinal fluid.

Botulinum Toxin Treatment

Several studies have reported the efficacy of botulinum toxin treatment in PHN. Among them are two high quality class I investigations (see definition in Chap. 2) that have demonstrated substantial improvement of pain in a high percentage of patients after injection of botulinum toxin A into the affected skin [9, 10]. In these studies subcutaneous injections of botulinum toxinA are given into 12 to 20 sites in the painful area pointed out by the patient. The injections are given through a short (¾ inch), thin (gauge 30) needle. Since injections are uncomfortable due to the skin sensitivity, an anaesthetic cream (Emla) may be applied an hour before the injections. The skin may be further numbed by an anaesthetic spray during the injections. The Botox dose per injection site is small, 2.5–5 units, for a total dose of 20–200 units depending on the extent of skin involvement. The pain relieving effect of Botox appears in 3 to 5 days and can last for 3 or more months. If shingles involves the face, the dose and number of injections need to be limited to minimum in order to avoid facial weakness. This is, however, an uncommon side effect since the injections are not into the muscles and the injection dose per site is very small. The facial weakness, if it developes, is mild and always disappears witin 2–3 months.

Sample Case

A 62-year-old female presented with severe pain behind the left ear of nearly 2 years duartion. Two years ago, she had developed shingles which was characterized by skin lesions in the back of the head and behind the right ear. The affected area was painful and the pain intensified by the passage of time. The pain was described as jabbing and stabbing, resulted in loss of sleep and prompted marked apprehension in anticipation of the next bout. Many pain episodes were described as "torture and unbearable." Treatment with a medication against herpes virus (acyclovir), improved the skin lesions but did not alter the pain. More severe bouts of pain were followed by disabling headaches. Pain killers such as gabapentin, pregabalin and oxycodone offered little help.

The patient was referred to Yale University Botulinum Toxin Clinic where her examination showed residual scars of zoster infection behind her left ear. The skin on this area was sensitive to touch. A total of 60 units of Botox was injected in a grid- like pattern under the skin, behind the left ear, at 20 points (3 units/point), using a thin 30- gauge needle (Fig. 5.3). The botox dilution was 100 units per 2 cc of saline. Patient reported a sharp drop in pain frequency and intensity 5 days after the injections. The pain then disappeared at week 2 post-injection, but gradually returned at 2.5 months post-injection. Over the next 2 years following the first treatment, patient received Botox injections every 3–4 months. During the third year, pain relief after Botox injections lasted 6 months. In her last follow up (4 years after the first treatment), she had no pain for 9 months and the returned pain was described as subtle and insignificant. She was very pleased with the outcome.

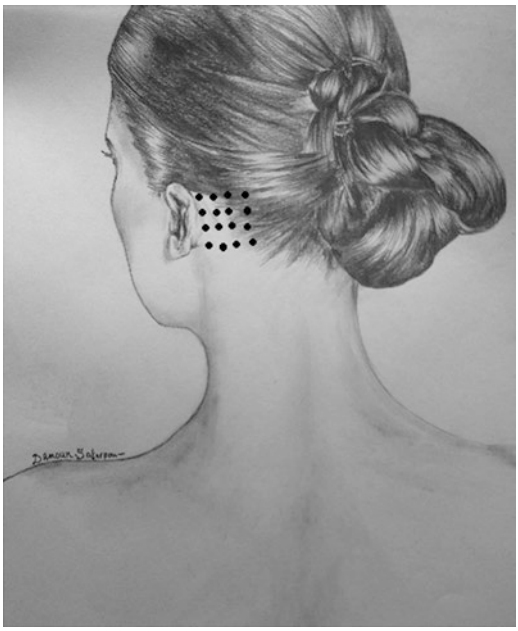

Fig. 5.3 Site of Botox injections for patient with post-herpetic neuralgia described above. Drawing, courtesy of Damoun Safarpour M.D.

Trigeminal Neuralgia (TN)

This term applies to facial pain that is felt in the distribution of trigeminal nerve. The trigeminal nerve, the fifth cranial nerve (one of 12 cranial nerves that supply the eyes, tongue, throat, head and face), is a pure sensory nerve. It supplies sensation of the upper, middle and lower face regions. The pain of TN is sharp, jabbing and short lasting but may occur many times during the day and unnerve the patient. It is usually felt on one side of the face but it may be felt in the gums and inside the mouth as well.

Trigeminal neuralgia is usually a problem of middle or old age and rarely affects young people. It has a prevalence of 4/100,000 in the US [11]. When it rarely develops in individual younger than 40 years of age, multiple sclerosis or a tumor at the base of the brain (brain stem) should to be suspected. Among older individuals, the cause of TN in most cases (older people) is believed to be age related degeneration of the trigeminal nerve. Treatment is medical and surgical. Medical treatment includes medications which are commonly used for treatment of epilepsy such as carbamazepine (Tegretol) and Gabapentin (Neurontin). Although medical treatment provides relief to many patients, over half, are not happy with the level of their pain relief. Surgery includes opening the back of the head and separating the nerve from the vessel. It is effective, but the pain can recur while the surgical procedure itself is a major task with potential serious side effects such as loss of hearing and balance. Gamma knife surgery is a newer approach and is performed with some degree of success in patients with TN.

Botulinum Toxin Treatment

Two high quality class I (see definition in Chap. 2), double blind, placebo controlled studies have demonstrated the efficacy of botulinum toxin therapy in management of trigeminal neuralgia [12, 13]. Both investigations have used a Chinese botulinum toxin (Prosigne). Prosigne's units are believed to approximate Botox's units. The investigators in both studies injected the involved skin of the face in a grid- like pattern at 12–16 sites. Injections not only improved pain but also significantly improved the patients' quality of life. The second study [13], compared the results of low dose (25 units) with high dose (75 units) of Prosigne for pain relief in TN. The authors concluded that 25 units is as effective as 75 units for pain relief and suggested using the low dose of 25 units in order to avoid facial weakness. This author has injected 8 patients with PHN with Botox using a method similar to that described above. Six of the eight patients experienced a satisfactory response.

Sample Case

A 41 -year old female complained of severe, intermittent jabbing pain in the left face for 9 months. The pain involved mainly the middle of the face, but often radiated to the left ear. It lasted 5–30 s, but recurred frequently sometimes 5–10 times/day. Treatment with different pain killers offered no relief. Injection of Botox into the left side of her face at 12 points (2 units per point- Fig. 5.4) resulted in marked reduction of pain frequency (from 3–4/day to 1–2/month). The recurring pain was considerably lighter in intensity compared to its predecessors. Repeated injections every 4 months had the same effect.

Diabetic Neuropathy

Neuropathy means a diseased peripheral nerve. Diabetes can damage peripheral nerves and cause diabetic neuropathy. Diabetic neuropathy affects 25–26% of individuals with type II (late onset) and 16% of individuals with type I (young onset) diabetes [14]. Patients with diabetic neuropathy complain of pain, numbness and, in advanced cases, weakness in the feet or hands. These symptoms are more prominent in the lower limbs. The skin in the affected areas is sensitive to touch (hyperesthesia) and sometimes touch evokes pain (allodynia). Pain may develope spontaneously and

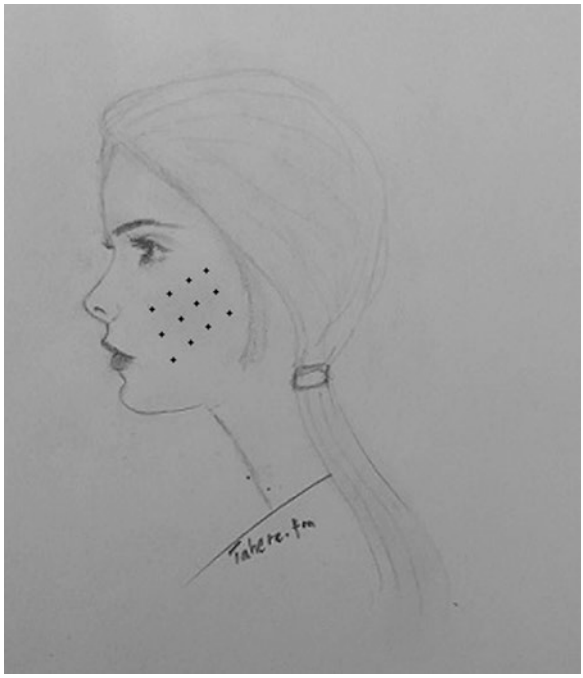

Fig. 5.4 Site of Botox injections in the patient with trigeminal neuralgia. Drawing,courtesy of Tahereh Mousavi, M.D.

interfere with patients, rest and sleep. The pain of diabetic neuropathy has the characteristic of a neuropathic pain. Neuropathic pain is sharp and burning and is often associated with allodynia. Dorsum of the foot and toes are most commonly affected in diabetic neuropathy. On examination, the patients often demonstrate decreased sensations (heat, cold, touch, position) in the affected limb. Diabetic neuropathy is usually bilateral and involves both sides. Treatment of diabetic neuropathy consists of avoiding sugar, lowering blood sugar levels with medications and treating pain when present. Mild cases of painful neuropathy can be managed by over the counter pain killers, whereas more severe cases require medications with recognized efficacy in neuropathic pain syndromes. Neurontin (gabapentin) and pregabalin (lyrica) are often used for this purpose. More severe cases are poorly responsive to these medications.

Efficacy of botulinum toxins in diabetic neuropathy has been the subject of several investigations. Two blinded studies one with Botox and one with Dysport (another type A botulinum toxin) have shown significant pain relief after botulinum toxin therapy [15, 16]. Injections are performed with a thin and short needle (less than one inch in length and gauge 30) in a gride- like pattern often covering the dorsum (top) of the foot and dorsal aspect of the toes (Fig. 5.5). Each unit of Botox approximates 2.5–3 units of Dysport. In many indications of botulinum toxin therapy if the first injection proves effective the efficacy continues with subsequent injections (usually every 3–6 months). Longterm efficacy data are not available for botulinum toxin treatment in diabetic peripheral neuropathy.

Plantar Fasciitis

Plantar fasciitis is related to damage to the plantar fascia(PF) from repeated trauma. Repeated trauma (running, certain sports and jobs)) can cause micro-tears in the plantar fascia with concurrent inflammation. Plantar fascia is a superficially located

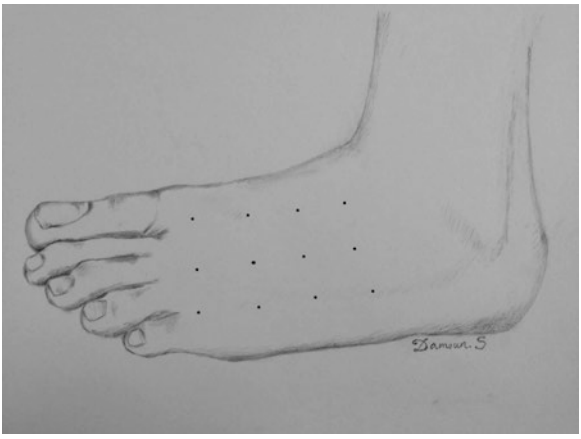

Fig. 5.5 Technique of skin injection for painful peripheral neuropathy in diabetic patients (Yuan and coworkers) [15]. Injetions are perfomed on both feet. Drawing, courtesy of Damoun Safarpour M.D.

layer of fibrous tissue (just under the skin of the sole of the foot) that connects the medial part of the heel to the base of the toes (Fig. 5.6). It is thickest (over 3 cm), close to its origin at the heel and it thins out as it approaches the toes. When it gets close to the toes, plantar fascia divides into 5 segments each connecting to the base of one toe. Under the PF, are located three muscles that flex the toes, one for three middle toes, one for big toe and one for the small toe.

Damaged plantar fascia causes pain that is felt most often in the heel(s), but also sometimes at the bottom of the feet. Pain can be felt during exertion or after a period of rest. It can be severe, impair the quality of life and interfere with sleep. In many patients, stopping the responsible activity (running, long distance walking) improves the condition and pain gradually subsides. Other patients with plantar fasciitis, however, may continue experiencing pain despite stopping the responsible activity or a job that requires continuing heavy foot works (i.e football players). Plantar fasciitis is a common problem that affects 10% of all runners and over two million people in the US [17].

Treatment starts with simple measures such as stretching, taping, night splints, orthosis, non-steroidal anti-inflammatory medications. In more persistent cases, steroid injections, ultrasound therapy, application of shock waves, acupuncture and cryosurgery (with freezing probes) are used. Unfortunately, the positive effect of these measures is often short lived. Furthermore, some of these therapeutic approaches are painful and hard to tolerate (i,e. shock wave therapy), while

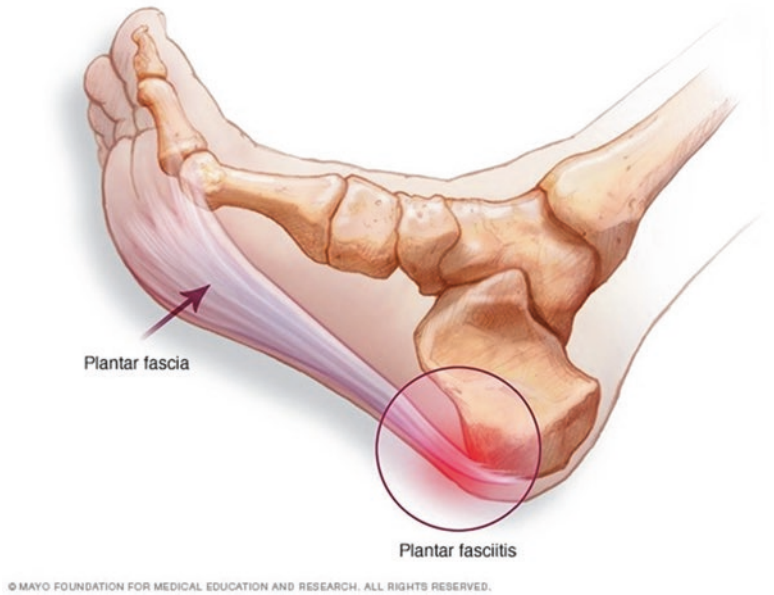

Fig. 5.6 Planter fascia and the area of pain (in red) in plantar fasciitis- From Mayo Foundation. Reproduced with permission

injection of steroids can cause rupture of the plantar fascia and make the situation more complicated. Clearly, an effective and safe treatment approach with less side effects is desirable for management of severe forms of PF.

Botox Treatment of Plantar Faciitis (PF)

This author and his co-workers have conducted the first prospective, placebo controlled, blinded investigation on the efficacy of Botox in plantar fasciitis at the Walter Reed Army Medical Center (WRAMC) in Washington D.C [18]. Twenty seven patients with plantar fasciitis and chronic symptoms (lasting >6 months) completed the study. Study subjects received either botox (70 units) or placebo (saline), 0.7 cc into two sites: 1- medial part of the heal(s), origin of PF (if Botox 40 units, if saline 0.4 cc)), 2- into the bottom of the foot, at mid-point, between the heal and base of the toes (if Botox 30 units, if saline 0.3 cc)). Efficacy of the treatment was measured at 3 and 8 weeks following injections. The group that received botox injections improved in several measures compared to the placebo: Maryland Foot Score ($P = 0.001$), Pain Relief measuref by Visual Analog Scale ($P < 0.0005$), and the pressure algometry response ($P = 0.003$). No side effects were noted. In 2010, Huang and co-workers [19], using a similar technique and a total dose of 50 units (Botox), reported very similar results in a blinded study of 50 patients with plantar faciitis. Díaz-Llopis and coworkers [20], compared the efficacy of Botox injection in plantar fasciitis with a combined steroid (betamethasone) and lidocaine injection in plantar fascitis. One month after injections, both groups described pain relief which was more notable among patients who had received Botox. At 6 months post-treatment, patients who had received Botox were still satisfied with the level of pai nreief, whereas patients who had received steroids developed recurrent pain. More recently (2017), improvement of pain and foot function was reported in patients with PF following Xeomin (another type of botulinum toxin A) injections into the painful sites of the foot [21]. Current literature indicates that botulinum toxin A (Botox or Xeomin) injections can relieve pain in plantar fasciitis and this treatment is more effective than steroid injections while producing less side effects.

Sample Case

A 73 year-old man had noted discomfort at the bottom of his feet, 7–8 years prior to a visit to the Yale Botulinum toxin treatment clinic. He was an avid tennis player who felt the most discomfort on the days that he played longer games. The discomfort gradually changed to pain which was felt at the heels, around the medial part of both feet. Over the years, he had tried a variety of treatments including stretching, orthosis, night splints, non-steroidal anti-inflammatory drugs, sessions of acupuncture and steroid injections. The latter two had helped some, but the results were

short lived. He stated having more "bad" days recently during which the heel pain was severe and quite uncomfortable.

His neurological examination was normal. Botox was injected into both feet using the methodology described above. A total of 70 units was injected −40 units close to the heel and 30 units at the bottom of the foot (Fig. 5.7).

Within days, the patient reported significant improvement of his heel pain; the pain relief lasted for 7 months. The second treatment also produced pain relief for 7–8 months. For the third and fourth treatments, an additional 30 units of Botox was injected into the soleus muscle which is located at the back of the lower leg and flexes the foot down via its attachment to Achilles tendon. It is often found to show increased tone in patients with PF. The third and fourth injections provided longer pain relieves (9–10 months). Patient reported no side effects.

Piriformis Syndrome (PS)

The pain in piriformis syndrome is related to tightness of piriformis muscle which is located deep in the buttock under gluteal muscles (large buttock muscles). Tightness of the triangular piriformis muscle can cause pain deep in the buttock due to its proximity to the sciatic nerve roots. The pain of piriformis muscle can be

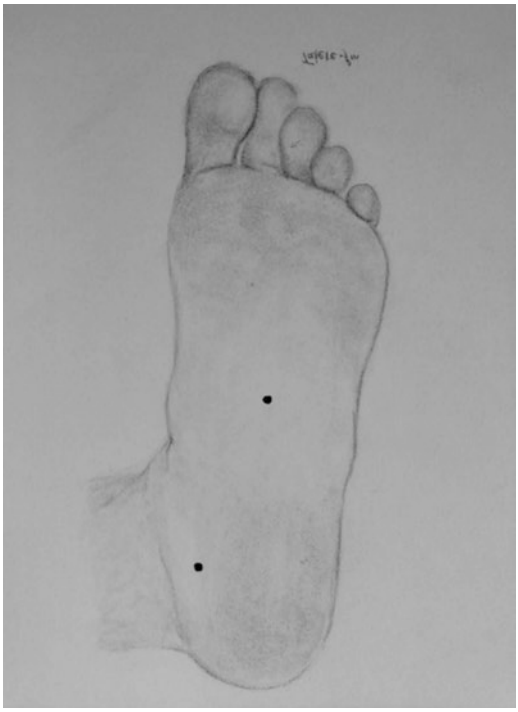

Fig. 5.7 Sites of Botox injection in plantar fasciitis. Drawing, courtsy of Tahereh Mousavi, M.D.

confused sometimes with low back pain due to a disc radiating to the thigh or with sciatica resulting from the irritation of the sciatic nerve further down in the thigh.

Botox injection into piriformis muscle has been shown to improve pain resulting from the piriformis syndrome. The largest placebo control study was conducted by Fishman and co-workers who compared the results of Botox, lidocaine and placebo injections into the piriformis of patients with PS. Pain relief was noted in 67%, 32% and 6% of the three groups respectively [22]. The technique of injection is laborious and needs to be performed under electromyographic guidance, to ensure proper insertion of the injecting needle. Electromyography records the electrical activity of the muscle, and in case of piriformis syndrome often demonstrates abnormal muscle activity. For injection, a special hollow needle is used that both records the muscle activity and allows injection of botulinum toxin through its core. Unlike for most indications of botulinum toxin therapy which utilize a short needle (¾ to 1 inch), a long needle, 4.5 to 5 inch, is needed for injections in PS in order to reach the deeply located piriformis muscle (Fig. 5.8).

There are several other pain syndromes in which there is scientific evidence for efficacy of botulinum toxin therapy. These include pain in arthritis, pain associated with peripheral nerve or spinal cord trauma, muscle pain associated with stroke, bladder and pelvic pain and pain associated with certain childhood surgeries. These areas will be discussed in the succeeding chapters of this book in relation to different diseases.

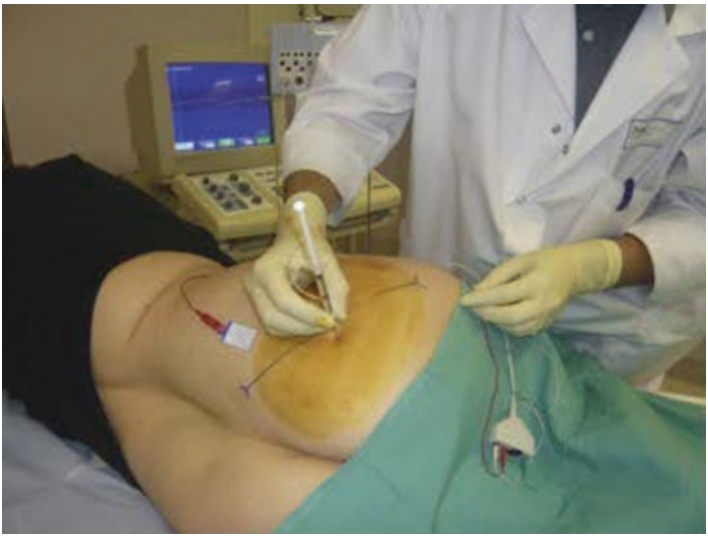

Fig. 5.8 Technique of botulinum toxin injection into the piriformis muscle. Michel and co-workers 2013- Reproduced with permission from the publisher Elsevier Masson SAS

Conclusion

Botulinumtoxins are helpful in relieving chronic pain in several pain syndromes. Botulinumxtoxin therapy in pain syndomes is safe and effective in the recommended doses.

References

1. Cui M, Khanijou S, Rubino J, et al. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107:125–33.
2. Marino MJ, Terashima T, Steinauer JJ, et al. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155:674–84.
3. Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. Toxicon. 2000;38:245–58.
4. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012;61:236–9.
5. Marino MJ, Terashima T, Steinauer JJ, et al. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155:674–84.
6. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. Neurology. 2001;56:1290–3.
7. Machado D, Kumar A, Jabbari B. Abobotulinum toxin A in the treatment of chronic low back Pain. Toxins (Basel). 2016, Dec 15;8(12). pii: E374
8. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007;82:1341–9.
9. Xiao L, Mackey S, Hui H, Xong D, Zhang Q, Zhang D. Subcutaneous injection of botulinum toxin a is beneficial in postherpetic neuralgia. Pain Med. 2010;11:1827–33.
10. Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin A in postherpetic neuralgia: a parallel, randomized, double-blind, single-dose, placebo-controlled trial. Clin J Pain. 2013;29:857–64.
11. Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. Ann Neurol. 1990;27:89–95.
12. Wu CJ, Lian YJ, Zhang YK, et al. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32:443–50.
13. Zhang H, Lian Y, Ma Y, et al. Two doses of botulinum toxin type a for the treatment of trigeminal neuralgia: observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. J Headache Pain. 2014;15(1):65.
14. Barrett AM, Lucero MA, Le T, Robinson RL, Dworkin RH, Chappell AS. Epidemiology, public health burden, and treatment of diabetic neuropathic pain: a review. Pain Med. 2007;8(Suppl 2):S50–62. Review
15. Yuan RY, Sheu JJ, Yu JM, Chen WT, Tseng IJ, Chang HH, Hu CJ. Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. Neurology. 2009;72:1473–8.
16. Ghasemi M, Ansari M, Basiri K, et al. The effects of intradermal botulinum toxin type a injections on pain symptoms of patients with diabetic neuropathy. J Res Med Sci. 2014;19:106–11.
17. Kibler WB, Goldberg C, Chandler TJ. Functional biomechanical deficits in running athlitis with plantar fasciitis. Am J Sports Med. 1991;19:63–71.
18. Babcock MS, Foster L, Pasquina P, Jabbari B. Treatment of pain attributed to plantar fasciitis with botulinum toxin a: a short-term, randomized, placebo-controlled, double-blind study. Am J Phys Med Rehabil. 2005;84:649–54.

19. Huang YC, Wei SH, Wang HK, Lieu FK. Ultrasonographic guided botulinum toxin type A treatment for plantar fasciitis: an outcome-based investigation for treating pain and gait changes. J Rehabil Med. 2010;42:136–40.
20. Díaz-Llopis IV, Rodríguez-Ruíz CM, Mulet-Perry S, Mondéjar-Gómez FJ, Climent-Barberá JM, Cholbi-Llobel F. Randomized controlled study of the efficacy of the injection of botulinum toxin type A versus corticosteroids in chronic plantar fasciitis: results at one and six months. Clin Rehabil. 2012;26:594–606.
21. Ahmad J, Ahmad SH, Jones K. Treatment of plantar fasciitis with botulinum toxin. Foot Ankle Int. 2017;38:1–7.
22. Fishman LM, Anderson C, Rosner B. BOTOX and physical therapy in the treatment of piriformis syndrome. Am J Phys Med Rehabil. 2002;81:936–42.

Chapter 6
Botulinum Toxin Therapy for Complications of Stroke

Introduction

Stroke is due to occlusion or rupture of a blood vessel in the brain. Occlusion of blood vessel acutely deprives a part of the brain from nutrients and oxygen, whereas rupture of a vessel destroys the brain tissue and replaces a part of the brain by a blood clot. Close to 90% of all strokes are caused by occlusion of a blood vessel. Brain's function is highly dependent on its blood supply which provides brain with oxygen. Brain uses oxygen more than any other organ in the body. Brain cells are very sensitive to lack of oxygen which can result in their death within a few minutes. Each year, over 800,000 people in the US suffer from stroke [1]. Stroke is the fourth cause of mortality world -wide and the first cause of adult disability in the US [2].

Acute impairment of brain function or lack of it leads to a variety of neurological deficits. The type of deficit depends on the region of the of the brain disabled by stroke. In small strokes recovery may be quick and sometimes complete. Unfortunately, most strokes result in a sizeable deficit with incomplete recovery despite the best medical treatment.

The most common and often the most disturbing of all mishaps after stroke is impairment of muscle function. Depending on the severity of the stroke, the aftermath of most strokes is some degrees of muscle paralysis. Our muscles function based on the nerve signals that they receive from the brain. In human, the brain is extremely well developed and has a larger size per body weight compared to much larger primates. Human brain contains approximately 86 billion nerve cells (neurons) and almost the same number of non-nerve cells (supporting cells-glia) [3]. The most superficial layer of human brain is called cortex. Cortex which is only 3–4 mm thick, consists of 26 billion nerve cells. Many of these cells are located in the motor region of the cortex which governs the motor function and controls the muscles (Fig. 6.1).

The large nerve cells that are located in the motor region of the cortex, send the motor command through their long processes (axons) to another motor cell in the

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_6

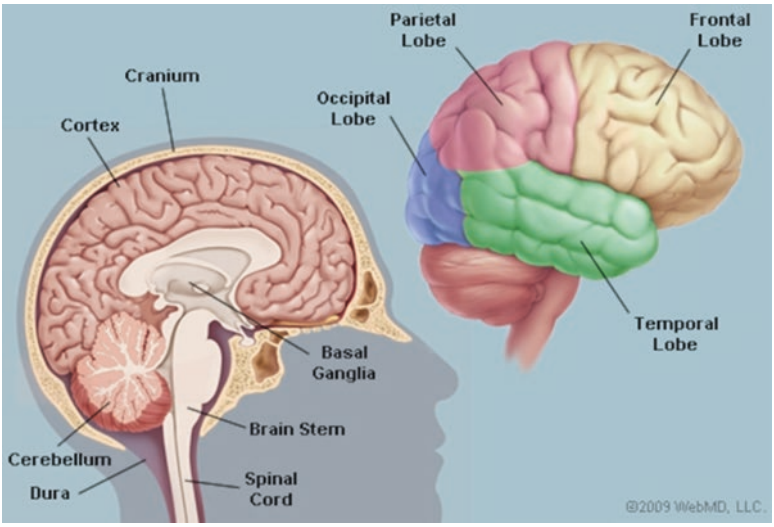

Fig. 6.1 The primary motor area is the most posterior and the primary sensory area is the most anterior part of frontal and parietal lobes, respectively. Reproduced with permission from WebMD

spinal cord and then to the muscle. This is unlike the cells in the sensory system, that covey the sensory signals from the skin to the brain. In the sensory system, at least two other sensory cells (one in the spinal cord and one higher up inside the brain) are contacted before the peripheral sensory signal reaches the sensory cortex. Each motor cell has one axon, a long fiber that conveys the message of the cortical nerve cell to motor cells in the spinal cord. The axons of the motor cells in the spinal cord convey the motor message to the muscle. Each axon of spinal cord motor cell when nears the muscle divides to several branches, each connecting to one muscle fiber. The point of contact between an axon and a muscle fiber is called neuromuscular junction. A neuromuscular junction has a axon part and a muscle fiber part with a cleft between the two structures (synaptic cleft) (Fig. 6.2). Since botulinum toxins relieve many muscle-related symptoms through their action on neuromuscular junction, the structure of neuromuscular junction and mechanism of muscle activation is described in more detail below.

The end of each axon (axon terminal) contains many vesicular structures, filled with a chemical called acetylcholine (Fig. 6.2). Acetylcholine is one of many chemicals that are considered neurotransmitters. This particular neurotransmitter's main function is conveying the nerve message to the muscle. The motor command from a cortical nerve cell travels along the axon to the periphery in form of an electric signal. When the nerve signal from the brain reaches the axon terminal next to the muscle, it activates a set of proteins in the axon terminal. Activation of these proteins ruptures the vesicular structures and releases their content (acetylcholine) into the synaptic cleft. The released acetylcholine attaches itself to muscle receptors (located on the surface of the muscle), excites, activates and contracts the muscle fiber.

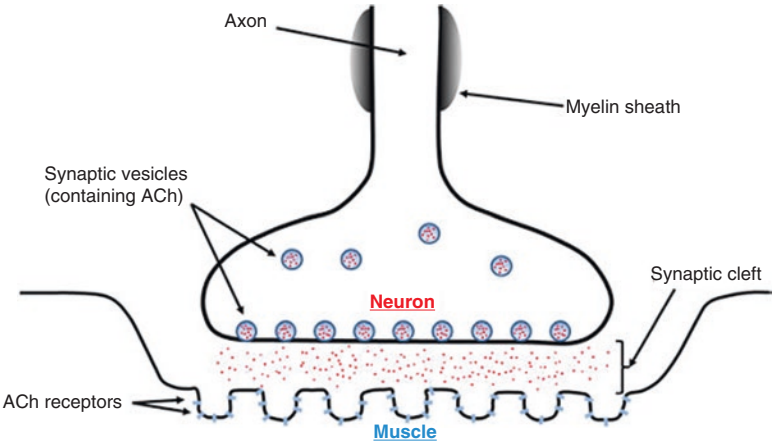

Fig. 6.2 Neuromuscular junction – The end of the motor axon (axon terminal) which faces the muscle fiber encompasses vesicles that contain acetylcholine (AC)

In stroke, in addition to paralysis which is the result of loss of nerve cells, degeneration and death of many axons and its terminal connections to muscle fibers results in a cascade of complicated events that leads to significant increase of tone in the weak muscle. This increased tone, leads to stiffness of the muscle and causes further functional disability. The increased tone of the muscle which is often associated with increased reflexes is called spasticity.

Spasticity After Stroke and the Role of Botulinum Toxins in Treatment of Stroke– Related Spasticity

Spasticity is a major handicap to patients who have suffered from stroke. Between 20 to 40% of patients with stroke develop spasticity within 1–6 weeks after the onset of stroke. Spastic muscles have limited range of motion and lack speed of function and precision. In the lower extremities, spasticity interferes with proper balance and ambulation.

Why the muscles of a weak limb after stroke gradually develop increased tone and become spastic has been the subject of extensive research. Brain both excites and inhibits the muscle activity through a set of complex mechanisms. Hence, enhanced excitation or reduced inhibition both can cause abnormally increased muscle tone and muscle spasticity. We have mentioned above the chemical acetylcholine that is present at nerve endings and upon release, excites the muscle. Inhibitory fibers that influence the muscle, work through their own inhibitory chemical (transmitter). Currently, there is strong evidence to support that disruption of these inhibitory fibers via tissue damage caused by stroke, plays a major role in development of spasticity.

Spasticity is not a benign complication of stroke. In addition to impairing balance and interfering with ambulation, spastic muscles can continue to harden and end in a state of continued contraction (contracture) leading to pain and immobility if not properly treated (Fig. 6.3).

Aggressive physical therapy, such as induced movement therapy, stretching, dynamic elbow-splinting and occupational therapy offer some help and can delay development of contracture to some extent. A large number of medications are used for reducing the tone in the spastic muscles, among which, baclofen, benzodiazines (valium), tizanidine and dantrolene are the most commonly used. These medications, although partially effective, are beset by undesirable side effects which limit increasing their dose to the optimal level (Table 6.1).

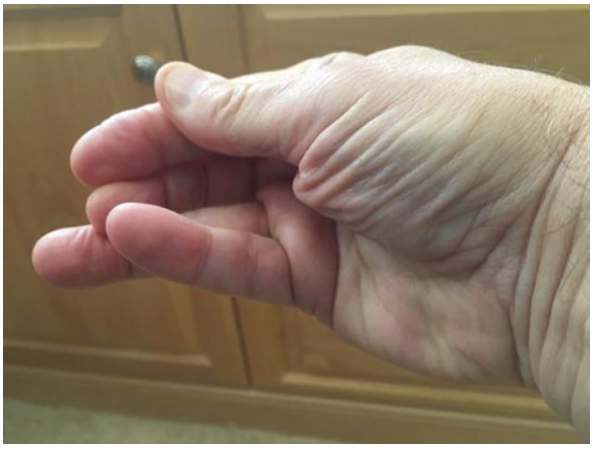

Fig. 6.3 Contracted and spastic muscles leading to contracture and loss of fingure function

Table 6.1 Medications commonly used for treatment of spasticity

Medication	Dose	Side effects
Valium	2–10 mg;3–4 times daily	Drowsiness, sedation impaired balance. Drop in blood pressure
Baclofen	Initial dose 5 mg, two to three times daily. Can be increased	Drowsiness, nausea, muscle weakness, confusion, seizures
	Every 2 to 3 days by 5 mg increments up 50-60 mg daily	
Tizanidine	Initial dose: 2–4 mg orally every 6–8 h	Sedation, drop in blood pressure, liver toxicity
	Maximum dose: 36 mg/day (12 mg, three times daily)	
Dantroline	Initial dose 25 mg once daily	Drowsiness, weakness, fatigue, liver toxicity
	Maximum dose: 100 mg, three times daily	

In severe lower limb spasticity, pharmacological treatment is often not very effective. Insertion of baclofen pump can reduce lower limb spasticity. This is an involved procedure that requires insertion of a small pump surgically into the abdominal wall. A catheter that emerges from the pump delivers a carefully titrated amount of baclofen into the cerebrospinal fluid (flowing inside that spinal canal) of the patient. This treatment requires facilities with experienced surgeons to insert and titrate the dose of baclofen in the pump. Inappropriate titrations can lead to severe side effects such as seizures and depressed level of consciousness. Other non-pharmalogical treatments of spasticity include repetitive electrical stimulation of the nerves and magnetic stimulation of the motor cortex with a specially designed magnet. Both procedures have a modest effect and are uncomfortable for the patient.

Botulinum Toxin Treatment of Spasticity

Botulinum toxins inhibit the release of acetylcholine from nerve ending, an agent that normally activates the muscle and in abnormal conditions may intensify the muscle contraction. This unique function makes the botulinum toxins effective therapeutic agents for treatment of hyperactive muscle disorders including spasticity. The commercially available toxin preparations are now used widely for treatment of a variety of neurological disorders [4].

As described earlier in Chap. 3, of the seven recognized serotypes of botulinum toxins, only types A and B are of clinical use due to their long duration of action (3–6 months). This long duration of action after a single injection is an advantage over oral medications which need to be taken daily. Three type A toxins are approved by FDA for use in the US with the trade names of Botox, Xeomin and Dysport. One type B toxin, Myobloc, is approved by FDA and is currently available in the US Market. The doses of these toxins are not comparable or interchangeable but in clinical and comparative studies the following approximations are used:

1unit of Botox = 1 unit of Xeomin = 2–3 units of Dysport = 40–50 units of Myobloc.

Spasticity not only pertains to stroke but can also be seen after brain and spinal cord trauma, in association with multiple sclerosis and in children with cerebral palsy. Following a large number of animal studies that showed reduction of muscle tone in animal models of spasticity after intramuscular injection of botulinum oxins, significant interest has developed among neuroscientists, neurologists, physiatrists and pediatricians for investigating the role of botulinum toxins in human spasticity. Early investigations focused on the role of botulinum toxin therapy in upper limb spasticity. These investigations looked at many facets of upper limb spasticity and aimed to answer many questions:

Can injection of Botulinum toxin (Botox, Xeomin, Myobloc, Dysport) into spastic muscles reduce muscle tone in human and improve the patient's quality of life?

Does reduction of spasticity of hand, forearm and shoulder muscles relieve the burden of caregivers and help physical therapy?

In other indications of botulinum toxins therapy such as involuntary, hyperactive muscles of face and neck, improvement lasts 3–4 months after muscle injection(s). Is this the case with spasticity?

Because of the size of muscles (considerably larger than face or neck muscles), larger doses of botulinum toxins are needed for injection into the affected muscle. Is injection of these higher doses in one session (for Botox up to 500 units for upper extremities) safe and devoid of serious side effects? How high of the dose can be used when both arm and leg muscles are injected?

To date 17 high quality studies have been published on Botulinum toxin effect on the spasticity of upper limb muscles, some of them including a sizeable number (in hundreds) of subjects [5, 6]. These studies collectively demonstrated that botulinum toxin injections into the tense and high tone muscles of stroke subjects reduced muscle tone, eased physical therapy and improved the patients' quality of life. Most patients were satisfied with botulinum toxin therapy and preferred this mode of treatment over taking large doses of daily medications. Serious side effects in spasticity studies were extremely rare and the toxin therapy was considered, in general, safe and practical. Based on the positive results of these studies, FDA first approved the use of Botox for treatment of upper limb spasticity in 2010. Subsequently, with availability of further studies, FDA approved the other two type A toxins, Xeomin and Dysport for treatment of upper limb spasticity in 2015.

One of the most feared complications of spasticity after stroke is development of muscle contracture. Contracture is loss and shortening of muscle fibers and replacement of muscle by non-elastic connective tissue. Contracture leads to total loss of muscle function and joint deformity.

There are some preliminary reports indicating that injection of botulinum toxin into the spastic muscle shortly after development of stroke can delay development of contracture. Further and higher quality studies are necessary to support these positive observations.

Muscle pain is another disturbing complaint of patients who develop spasticity after stroke. Pain is often measured on a scale of 0–10 (visual analogue scale). A value of over 4 is considered to represent a pain severe enough to interfere with daily activities. Patients with spasticity often have muscle pain. In a recent Canadian study Dr., Shaikh and his colleagues found that 65% of their patients with post-stroke spasticity had associated muscle pain[7]. The pain was more noticeable during movements. Most patients (80%) believed that their muscle pain was related to their stiff, spastic muscles. Following Botox injections, 62% of the patients reported pain relief within days after injection.

Lower limb spasticity after stroke can be very disabling. Spasticity adds to muscle weakness in stroke patients, limits leg movements and adds to difficulty with ambulation. High quality studies in lower limb spasticity, although fewer in number (six), also have shown reduction of tone and improvement of quality of life after botulinum toxin therapy. Some studies have clearly demonstrated that botulinum toxin injections into the leg muscles of patients with stroke improve ambulation.

Based on availability of these high quality studies, FDA approved the use of Botox and Dysport for adult lower limb spasticity in 2014 and 2017, respectively. Currently, Dysport is the only form of botulinum toxin approved for lower limb spasticity in children (FDA approval 2016).

Lower limb includes large muscles of the thighs that require more units of botulinum toxins in order to relax compared to hand or forearm muscles. Investigators wondered if injection of doses larger than that usually used for the upper limb muscles (up to 400–500 units of Botox or Xeomin), are safe to be given in one session to the lower limb muscles or in conditions that require treatment of both arms and legs. Furthermore, it is known that the larger the dose of the toxin, the higher the chance of antibody formation against the toxin, which upon development may nullify the toxin's therapeutic effect. Antibody formation is also enhanced by repeated injections which in case of spasticity are required to maintain the reduced tone in the spastic muscles of the stroke patients over time.

In regard to safety of larger doses, Dr. Wissel and his colleagues has recently published the result of a combined European- American investigation on 155 patients in whom doses of Xeomin (a botulinum toxin A with units similar to Botox) were escalated over months from 400 to 600 and then ultimately to 800 units per session of treatment [8]. Increasing the dose was more efficacious in reducing spasticity but did not increase the percentage or severity of side effects. Main side effects were diarrhea and minor throat infections, noted in 5% of the patients.

Several investigators have researched development of antibodies in patients who received large doses of botulinum toxin A over several years. These studies either did not find any antibodies or found antibodies in a very small percentage of the patients (< 0.4%) [5, 9]. The antibody research, therefore, indicates that with the latest formulation of botulinum toxins, antibody formation is not an issue of significance when botulinum toxin therapy is used for spasticity.

Technical Issues in Botulinum Toxin Treatment of Stroke Spasticity

All four of FDA approved botulinum toxins in the market (Botox, Xeomin, Dysport, Myobloc) have shown efficacy in treatment of post stroke spasticity, though the data on myobloc (type B toxin) is small compared to the other three toxins. In case of Botox, Xeomin and Dysport, the powder form of the toxin (provided in a small vial) needs to be mixed with salt water– saline, usually 2 ccs before injection. Myobloc is marketed in an already prepared solution form. Injections are often guided by electromyography, a device that identifies muscles by their electrical pattern. Also, location of the muscle can be identified by nerve stimulation. A nerve stimulator, stimulates a nerve which is known to serve a certain muscle and by doing so identifies the muscle (muscle moves in response to the stimulation). Ultrasound is a more precise way to localize and clearly visualize the muscles [10]. The technique however, requires a fair amount of expertise.

Upper limb, spasticity more often involves muscles that flex the joints. For instance, involvement of biceps muscle leads to abnormal flexion of the arm, a position that can interfere with dressing and use of the arm for other activities of daily living. This is often associated with wrist spasticity (flexed wrist) and sometimes with forced flexion of fingers causing "clenched fist." The latter two, when severe enough, can make the involved hand non- functional. In the lower limb, abnormal flexion of the knee or foot interferes with standing and ambulation. Flexion of the knee results from spasticity and high tone in the large hamstring muscles located on the back of the thighs. Botulinum toxin injections are usually carried into two to three points into the large muscles (Fig. 6.4). The units of toxin used per muscle depend on the size of the muscle (Table 6.2). The effect of botulinum toxin injection, appears in 3–7 days (muscles loosen) and the effect peaks in 2–3 weeks. The effect usually lasts for 3–4 months. Reinjections are required every 3 to 4 months to keep the spastic muscle in the state of reduced tone.

In clinical practice, in order to achieve best results, botulinum toxin therapy is often combined with physical therapy. Concurrent pharmacological therapy with anti-spastic drugs such as baclofen or tizanidine (see Table 6.1) may be required in cases of severe spasticity. Unfortunately, in elderly patients, these medications often cause undesirable side effects, the most disturbing among them are sedation and depressed level of consciousness. On the contrary, Botulinum toxin injections do not cause sedation or depress the level of consciousness (Fig. 6.4).

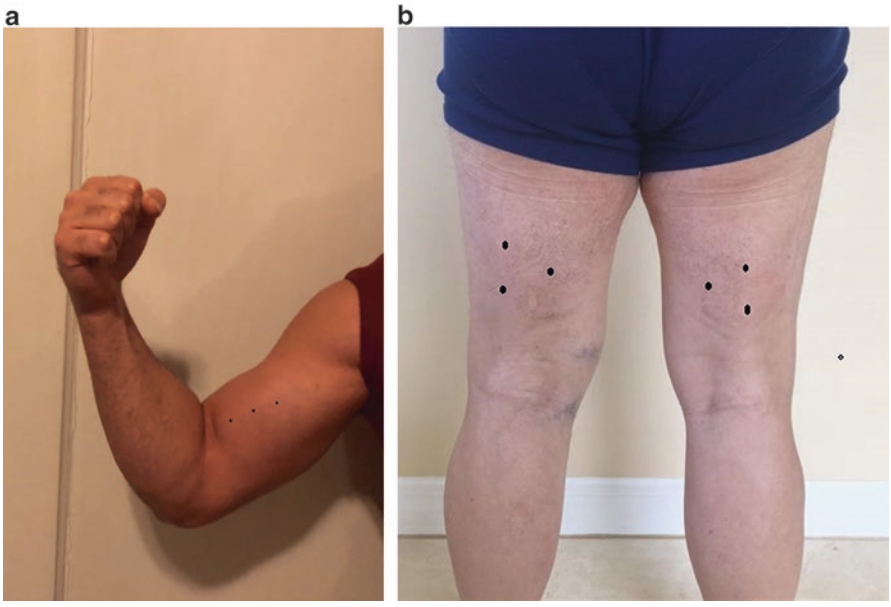

Fig. 6.4 Botulinum toxin injection of biceps (**a**) and hamstring (**b**) muscles. Each muscle is injected in three points. Courtesy of Dr. Damoun Safarpour

Table 6.2 Dose of Botox or Xeomin per muscle per side for some of the commonly injected muscles in stroke spasticity. For Dysport the dose can be multiplied 2.5–3 times and for Myobloc multiplied by 40 to 50 times

Muscle	Dose in units (Botox or Xeomin)
Biceps	60–100 Per muscle, per side
Triceps	60–100
Wrist flexors	40–60
Hamstring (knee flexor- back of the thigh)	60–200
Quadriceps (knee extensor- front of the thigh)	60–100
Gastrocnemius (foot flexor-back of the leg)	60–80

Botulinum Toxin Therapy of Persistent Drooling after Stroke

Drooling becomes an annoying problem in some patients after stroke. This is often due to paralysis of the face muscles which become unable to clear the saliva from the mouth. In such patients, reduction in saliva production would be desirable. It has been shown in both animals and human that injection of Botox and other botulinum toxins into the glands that produce saliva (parotid, sub-maxillary) reduces the production of saliva. This is also the case in patients who have drooling after stroke [11]. Injections are done with a very small needle. In case of parotid gland that are barely under the skin, a few milimeter penetration is sufficient. Usually 2 to 3 sites are injected within the gland, preferably under ultrasound visualization. Many clinicians inject without using the ultrasound machine since even without direct visualization of the gland, the yield of procedure is high and satisfactory to the patient. Injections take less than a minute and are associated with only mild discomfort. Numbing the skin is not necessary. Injections need to be repeated every 4–6 months. The chemical that conveys the nerve signal to the gland to initiate secretion of saliva is acetylcholine – the same chemical that activates the muscle. As was discussed earlier, botulinum toxins inhibit the release of acetylcholine at the nerve endings. Details of saliva secretion, anatomy of salivary glands and effects of botulinum toxins on saliva production are presented in chapter 13.

Botulinum Toxin Treatment of Joint Pain after Stroke

Immobility of the joints after stroke, caused by muscle paralysis, often leads to joint degeneration with subsequent chronic joint pain. As described in Chap. 5, botulinum toxins in addition to acetylcholine, also inhibit the function of a variety of pain transmitters. This inhibition of pain transmitters occurs in the peripheral nervous

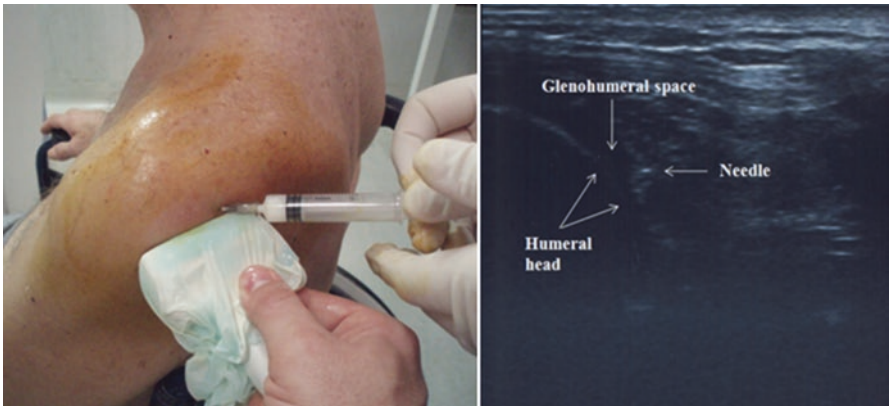

Fig. 6.5 Method of the shoulder joint injection in a patient with paralysis of the left arm after stroke and shoulder joint pain. The right side of the figure shows an ultrasound image that demonstrates the position of the injecting needle and the head of the long bone of the arm. From Castiglione and co-workers, printed with permission from Elsevier

system as well as in the central nervous system as the molecule of the toxin from the site of injection travels to the spinal cord and influences the sensory cells that convey pain to the brain. Injection of Botox (and other toxins) into the joints has been shown to alleviate joint pain in several of kinds of joint problems (Chap. 10 of this book, orthopedic indications). Chronic joint pain after stroke, specially pain in the shoulder joint, also responds to botulinum toxin injections into the involved joint (Fig. 6.5).

Movement Disorders After Stroke

A variety of involuntary movement can develop after stroke either due to damage to critical brain areas or damage to muscles that receive their nerves from the brain. Many patients with stroke demonstrate weakness of half of the face on the side of limb weakness. The weak eyelids or facial muscles sometimes develop bothersome and persistent involuntary twitches. Injection of small amounts of Botox into these muscles with a fine needle often suppresses the lid or facial movements for 3–4 months.

Dystonia is a movement disorder characterized by twisting and turning, flexion or extension of a joint leading to abnormal postures. Dystonia is a common movement disorder that may develop after stroke affecting the muscles opposite to the side of brain damage. In stroke patients, dystonia is often mixed with spasticity. Dystonia is one of the most responsive movement disorders to botulinum toxin therapy. Figure 6.6 shows dystonia of the neck and shoulder muscle developed after a stroke involving deep brain structures. The patient demonstrates head tilt to the

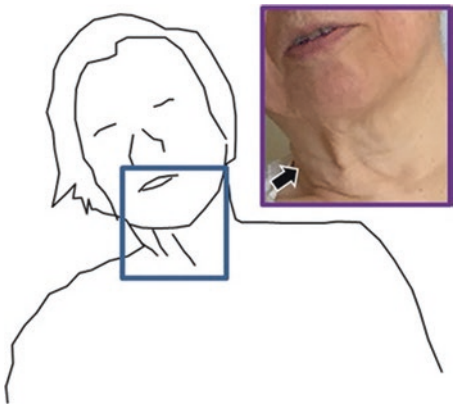

Fig. 6.6 Dystonia after stroke. From Ogawa et al. in journal of medical case reports 2018 – printed with permission from publisher – Biomed Central

right, slight neck rotation to the right flexion dystonia and pulled down right shoulder. Although in this patient dystonic posture improved gradually and spontaneously, if persistent botulinum therapy can be of significant assistance (see Chap. 11 – botulinum toxin treatment of dystonias and cervical dystonia).

Conclusion

Introduction of botulinum toxin therapy to clinical medicine has revolutionized the management of stroke related spasticity. Treatment of spastic muscles after stroke with botulinum toxins is effective and has improved the patients' quality of life. Recent data indicates safety of this treatment even with relatively high doses (up to 800 units for Botox or Xeomin). Botulinum toxin therapy also relieves the pain associated with spasticity or chronic joint pain in the paralyzed limb as well as reducing drooling and improving limb dystonia after stroke.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017;135:e146–603. https://doi.org/10.1161/CIR.0000000000000048.
2. Kochanek KD, et al. Deaths: final data for 2009. National vital statistics reports: from the centers for disease control and prevention, national center for health statistics, national vital statistics system. 2011;60: 1–116.
3. Herculana-houzel S. The human brain in numbers: a lineary scled up primate brain. Front Hum Neurosci. 2009, Nov 9;3:31. doi:https://doi.org/10.3389/neuro.09.031.2009. eCollection.
4. Jankovic J. Botulinum toxin: state of the art. Mov Disord. 2017;32:1132–8.

5. Kaku M, Simpson DM. Spotlight on botulinum toxin and its potential in the treatment of stroke-related spasticity. Drug Des Devel Ther. 2016;10:1085–99.
6. Moeini-Naghani I, Jabbari B. Botulinum toxin treatment in cerebrovascular disease. In: Jabbari B, editor. Botulinum toxin treatment in clinical medicine. Springer; 2018. p. 213–30.
7. Shaikh A, Phadke CP, Ismail F, et al. Relationship between botulinum toxin, spasticity, and pain: a survey of patient perception. J Neurol Sci. 2016;43:311–5.
8. Wissel J, Bensmail D, Ferreira JJ, et al. Safety and efficacy of Incobotulinum toxin A doses up to 800 U in limb spasticity. Neurology. 2017;88:1321–8.
9. Bakheit AM, Liptrot A, Newton R, Pickett AM. The effect of total cumulative dose, number of treatment cycles, interval between injections, and length of treatment on the frequency of occurrence of antibodies to botulinum toxin type A in the treatment of muscle spasticity. Int J Rehabil Res. 2012;35:36–9.
10. Alter KE, Karp BI. Ultrasound guidance for botulinum neurotoxin chemodenervation procedures. Toxins (Basel). 2017 Dec 28;10(1). pii: E18) https://doi.org/10.3390/toxins10010018.
11. Mazlan M, Rajasegaran S, Engkasan JP. A double-blind randomized controlled trial vestigating the most efficacious dose of botulinum toxin-A for sialorrhea treatment in Asian adults with neurological diseases. Toxins (Basel). 2015;7:3758–70.

Chapter 7
Botulinum Toxin Treatment in Multiple Sclerosis

Introduction

Multiple sclerosis is seen in 130–150/100,000 of the US population [1]. It affects over two million people world-wide and 400,000 people in the USA [2]. In US, the financial burden per person can be up to $52,000 per year [3]. In late nineteenth century, a famous French neurologist by the name of Charcot was the first to describe, in detail, the symptoms and the pathology of multiple sclerosis. Multiple sclerosis damages both motor and sensory nerve fibers; Motor fibers originate from brain cells and go to the muscles and the sensory fibers convey sensations from skin to the brain. These nerve fibers normally have a protective sheath on their surface that enhances the conduction of the electrical signals flowing in them both away and towards brain. This sheath of tissue that covers the nerves has a fat composition and is called myelin. Multiple sclerosis is, therefore, considered one of the diseases that specifically destroy myelin (demyelinating). Loss of myelin leaves scars in the brain and/or spinal cord. These scars are easily detected by modern imaging techniques such as MRI. Currently, MRI is a major diagnostic device used to confirm or support the diagnosis of multiple sclerosis (Fig. 7.1). These scars or plaques are often multiple and occur at different levels of the central nervous system, brain and/or spinal cord (multiple sclerosis). One can also use the changes that takes place in the composition of the cerebrospinal fluid (CSF) to support the diagnosis of multiple sclerosis. Cerebrospinal fluid is made in the brain and runs inside the spinal canal between the bones all the way from the upper neck to the low back area. To test CSF, a small amount of this fluid is removed for examination by a procedure called spinal tap. For spinal tap, after numbing the skin, a needle is placed at midline between two low back bones in the lumbar area. In most patients with MS, examination of CSF shows an elevation of certain specific proteins.

Multiple sclerosis can cause a variety of symptoms depending on the location of the lesions. A large number of patients complain of motor symptoms, such as sudden weakness or even total paralysis of one limb. Others may have sensory

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_7

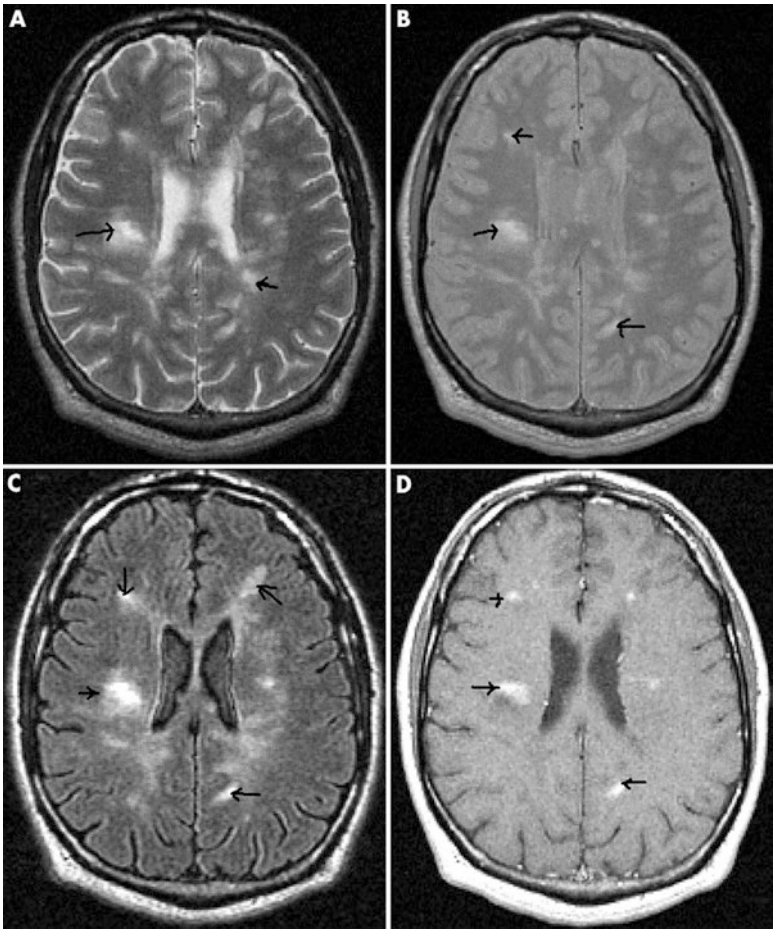

Fig. 7.1 Multiple brain lesions in a patient with multiple sclerosis. The lesions, white patches, marked by arrows in the brain slices on MRI, represent abnormal areas of the brain. From Trip and Miller 2005, reproduced with permission from publisher (BMJ group)

symptoms, often described as tingling and numbness affecting some part of the body. Sudden onset of diminished or even total loss of vision in one eye is also a frequent complaint. Symptoms of MS fluctuate in intensity, disappear and reappear over time. In chronic cases, scars accumulate in the brain or /and spinal cord and lead to permanent loss of function.

The cause of multiple sclerosis is still not fully understood. In current scientific thinking, multiple sclerosis is defined as an "autoimmune disease". Our immune system normally protects us against germs like viruses or bacteria. When body is exposed to foreign invaders, immune system sends a group of fighter cells to attack and destroy invaders. Usually, the immune system can differentiate between one's own cells and foreign cells. In an autoimmune disease, the immune system

mistakenly attacks the cells and organs of the body. The damage to nervous system in multiple sclerosis is believed to be due to this immune reaction which is associated with a lymphocytic reaction (certain blood cells) in this area.

In the past two decades, significant strides have been taken to find drugs that work against these immune reactions while aiming to arrest progression of MS and prevent appearance of new lesions in the brain. Several newly discovered drugs in this category have succeeded to slow the course of multiple sclerosis and prevent appearance of new brain lesions. Some of these drugs such as alemtuzumab and or daclizumab specifically work on the lymphocytes and the immune system. Unfortunately, despite these efforts, still a large number of patients with MS are left with permanent disabilities due to multiple damages sustained within the nervous tissue (brain and spinal cord) over years. Among these disabilities, stiffness of muscles (spasticity) and dysfunction of bladder can significantly impair the patients' quality of life. Research data and clinical experience have shown that both muscle spasticity and bladder dysfunction in MS, improve significantly with botulinum toxin injections into the involved muscles or into the bladder wall.

Botulinum Toxin Treatment of Spasticity in Multiple Sclerosis

In multiple sclerosis, similar to other disease conditions that damage the brain and spinal cord (stroke, trauma), weakened muscles gradually show increased tone, become stiff and spastic. In many patients with MS, this spasticity can be quite severe and interfere with the activities of daily living. The spastic muscle often remains contracted resulting in impaired timing and precision of movements. Using fingers and hands for eating, washing, shaving, dressing and any other fine movements becomes exceedingly difficult. In the lower limbs, spasticity adds to weakness and impairs balance. Adductor muscles of the thigh (muscles that bring the thighs together) often show marked spasticity in multiple sclerosis. As a result, sustained contraction of these muscles keeps the thighs always together, a position that impairs normal leg movements and ambulation. These patients complain of poor balance and frequent falls. As time goes by the spastic muscles become painful to move. The ensuing immobility leads to replacement of muscle fibers by non-elastic tissue, a condition that is termed contracture. Muscles affected by contracture are often shortened and non-functional.

The drugs that treat spasticity such as baclofen, tizanidine and valium often have undesirable side effects such a confusion and sedation. In severe cases of spasticity, especially if it predominantly involves the legs, baclofen can be delivered to the body through a baclofen pump. Use of baclofen pump is an involved procedure requiring insertion of a catheter into the spinal canal through which baclofen is continuously delivered into the spinal fluid. The procedure requires collaboration between an expert neurosurgeon, neurologist and a trained nurse expert who could do careful titration of the drug. Miscalculations can lead to overdosing, leading to serious complications such as suppressed level of consciousness and seizures. Other

severe cases of spasticity can be treated by injection of phenol into the nerve that supplies the tight and spastic muscles. Phenol injections are effective but reserved for very severe cases when all other means fail since such injections destroy the nerve permanently. Pharmacological treatments of spasticity are usually combined with physical therapy that includes passive and active exercises.

It is believed that 80% of the patients with multiple sclerosis will experience spasticity of muscles some time during their lifetime. In a large US registry of patients with multiple sclerosis, 72% of the patients demonstrated moderate to severe spasticity on examination [4]. Spasticity of multiple sclerosis is more prominent in the lower limbs. The adductor muscles of the thighs that bring the thighs together are often involved. Increased tone of these muscles may lock the thighs together causing difficulty with hygiene and ambulation.

Botulinum toxin treatment (with Botox and other variants) provides a reasonable alternative to pharmacotherapy. In general, botulinum toxins have less side effects than anti-spasticity drugs and require a set of injections (usually into 3–5 muscles) every 3–4 months. The effect of botulinum toxin injection on the muscle becomes manifest in 2–5 days and peaks at 2–3 weeks. The muscle relaxing effect of the toxin can last 3–4 months; this effect, is to a large degree, dose dependent.

Currently, four globally marketed botulinum toxins are approved by FDA for use in the US. Three of these toxins are type A (Botox, Xeomin and Dysport) and one toxin is type B (Myobloc – in Europe Neurobloc). For detailed description of toxin types and information on toxin characteristics the reader is referred to Chap. 3 of this book. Although the units of these four toxins are not exactly comparable, in clinical practice the following approximations are used:

1 unit of Botox = 1 unit of Xeomin=2.5 to 3 units of Dysport = 40–50 units of Myobloc.

In 1990, Dr.Snow, a Canadian investigator and his colleagues reported that injection of Botox into the adductor muscles of the thigh (muscles that bring the thighs together: Fig. 7.2a), significantly reduced the spasticity and improved hygiene in 7 out of 9 patients studied [6]. A total of 400 units of Botox was shared with three thigh adductor muscles. Several, subsequent high quality studies with much larger number of patients (in hundreds) have supported this observation. Furthermore, longterm observations over several years have shown that repeated injections at every 3 months are well tolerated and the satisfactory effects continues over months and years of treatment. These studies have also shown the safety of botulinum toxin therapy in this setting. Comparative studies have shown that MS- related spasticity is as responsive as any other form of spasticity (stroke, trauma) to the botulinum therapy and the effective dose per muscle in multiple sclerosis is comparable to that used for spasticity caused by medical conditions other than MS (stroke, trauma, etc). For this reason, botulinum toxin therapy is now among the first lines of treatment for spasticity in multiple sclerosis.

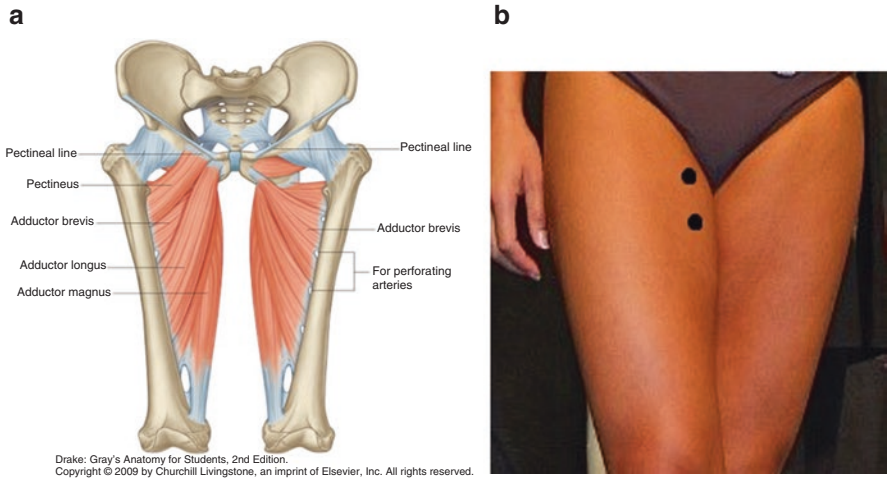

Fig. 7.2 (**a**) Three adductor muscles of the thigh that bring the thighs together; short (brevis), long (longus) and large (magnus). From Drake Anatomy for students printed with permission from elsevier. (**b**) A common site of botulinum toxin injection for adductor spasticity

Technique of Injection

The injection technique for thigh muscles of patients with multiple sclerosis is very similar to what has been described in Chap. 7 for stroke-related spasticity. The size of the muscle and the degree of tightness of the muscle determines the dose. The dose is delivered in units. In the upper limbs, for small muscles of the forearm and hand, the dose varies from 5–20 units per muscle, whereas larger muscles (i.e biceps) may require up to 100 units (Botox or Xeomin, for Dysport and myobloc, multiply the units by 2.5–3 and 40–50 units respectively). In the lower limb muscles, even larger doses can be used for instance up to 150–200 units for adductor muscles and even higher for large muscles in the back or front of the thigh that flex or extend the knee joint. The injecting needle is thin and short for upper limb muscles but longer for larger muscles of the lower limb. Injections are delivered at two or three sites into the each muscle, using anatomical landmarks for identifying nerve-muscle junctions (where injections are most effective). Recent studies have shown that larger doses of Botox or Xeomin of up to 800 units, can be injected in one session (into 3–5 muscles), without any serious side effects. Side effects include local pain at the site of injection for a few minutes, minor transient bleeding, and a mild, transient flu like reaction experienced in 10–15% of the patients. It should be remembered that toxin preparation needs to be done by trained personnel and injections should be carried out by experienced injectors familiar with the muscle anatomy and proper technique. Dose miscalculations can lead to serious side effects such as total paralysis and endanger patient's life.

Case Report

A 32 years-old female with multiple sclerosis was referred to the Botulinum Toxin Clinic for treatment of severe spasticity of the thigh muscles. For several years, she had suffered from severe tightness of her thigh muscles, the overactivity of which pulled her legs constantly together. Oral medications provided modest relief. She had difficulty sitting up and ambulating. The legs pulled together further during walking and impaired her balance. On examination, one could feel very tight adductor muscles on the medial aspect of the thighs close to the groin (Fig. 7.2b). She was injected with Botox into adductor muscles- 150 units/side (Fig. 7.2). After a week, she reported marked improvement of several of her functions. Relaxation of thigh muscles allowed her to stand and walk better and with less fear of falling. Moving in bed became easier, she slept better. Movement of the thighs was no longer painful. Hygiene related tasks were carried out with more ease and comfort. The satisfactory effects of Botox injection lasted for 3 months. She experienced the same positive response with repeated injections, every 3–4 months, over a follow up period of 5 years.

Botulinum Toxin Therapy for Bladder Problems in Multiple Sclerosis

Patient with multiple sclerosis develop a variety of bladder problems as the disease progresses. Bladder, as the organ of urine storage and emptying, functions mainly with three muscles. The major bladder muscle that controls storage and emptying function of the bladder is called detrusor muscle (See Fig. 7.1 in Chap. 6, bladder dysfunction). This muscle that spread over nearly all of the bladder wall can expand during urine storage. When the volume of urine in the bladder reaches a certain level, sensory nerves of the bladder signal the bladder centers located in different parts of the brain (there are more than one) to tell the detrusor muscle to contract. Detrusor muscle contraction propels the urine against the hole in the lower part of the bladder through which the urine leaves the bladder. Two circular muscles, called sphincters, control the opening and closing of this hole. The one closer to the inside of the bladder is called inner and the one further out is called outer sphincter. Inner sphincter automatically relaxes after contraction of detrusor muscle. This relaxation is not under conscious control. The outer sphincter is under conscious control and can be relaxed by will, letting the urine out in an appropriate setting. A complex network of nerve cells spread from brain to the spinal cord control the bladder function. As spinal cord nerve cells and nerve fibers are major contributors to the innervation of bladder, damage to the spinal cord in multiple sclerosis (with lesions similar to those seen in the brain-Fig. 7.1) results in erratic and poorly timed contractions of the detrusor muscle with subsequent development of bladder symptoms.

These symptoms include frequent urge to urinate and frequent urination, bed wetting at night and incontinence during the day. Poor emptying of the bladder predisposes the patient to development of bladder infections. In more severe cases, the urine can back up toward the kidney and cause kidney damage. The type of bladder dysfunction in MS is called neurogenic bladder i.e. a bladder problem that is related to damage to the nerve supply of the bladder.

Bladder symptoms are common in multiple sclerosis. A survey conducted by the North American Research Committee on Multiple sclerosis (NARCMS), found that 65% of patients with MS complained from moderate to severe bladder symptoms which include leakage, urgency, frequent urinations at night and urinary incontinence [7]. What happens to the bladder muscle in MS is somewhat similar to what happens to the neuromuscular junction leading to muscle spasticity as describd earlier in this chapter. The muscle (in this case detrusor muscle of the bladder), after being weakened by damage to its nerve supply, gradually develops increased tone, and as in other muscles of body with spasticity becomes overactive. Since acetylcholine is also the chemical transmitter (from nerve ending) to the muscular layer of the bladder, injection of botulinum toxins into the bladder wall will subdue the bladder overactivity by reducing the effect of acetylcholine (see Chap. 2 on mechanism of function of botulinum toxins). The drugs that are used for control of bladder symptoms in MS anticholinergics- Ditropan, Detrol - also work by reducing or blocking the effects of acetylcholine. The frequent side effects of these drugs, anticholinergics, such as blurring of vision, impaired memory and dryness of the mouth make them hard to tolerate especially over a long period of time.

In 2013, FDA approved the use of Botox for treatment of neurogenic, overactive bladder in multiple sclerosis based on the positive results of two large high quality, multicenter studies (DINGY studies) that investigated close to 700 patients with MS and spinal cord injury. These studies have shown that injection of 200 units of Botox at multiple points into the bladder wall significantly improves the patients' urgency and incontinence as well as their quality of life. Patients also scored highly on a post-treatment satisfaction questionnaire showing their satisfaction with treatment.

The main side effect of botulinum toxin injections for bladder symptoms in MS is retention of urine which occurs in 25% of treated patients and may require daily clean self-catheterization. In many patients with advanced MS, however, this was not problematic since they had already chronic urinary retention and were self-catheterizing themselves for months or years. Nevertheless, patients need to be alerted and trained for this side effect. Some recent studies have shown that with time, the incidence of urinary retention after Botox injection into the bladder goes down, 8% at third year and almost 0% by the fourth year of treatment. A recent analysis of 18 studies with 1553 MS patients in whom bladder dysfunction was treated with Botox injection into the detrusor muscle reported sustenance of positive results after repeated injections and a low incidence of side effects [8].

Injection Technique

Botox is marketed in a powder form stored in small vials. For all indications, it needs to be mixed with normal saline (salt water) before injection. Botox is very heat sensitive so it requires refrigeration. Botox vials usually contain 100 units. A total of 200 units is recommended for treatment of overactive bladder in multiple sclerosis. Injections are carried out through a special instrument, cystoscope, that after entering the bladder can visualize inside the bladder via a small light. A hollow needle is attached to the cystoscope through which the injections are performed. The original FDA approved protocol calls for 30 sites of injections sparing the trigone (the lower, triangular par of bladder- Fig. 7.3) of the bladder. Currently, however, different protocols are used at different institutions with the number of injections ranging from 20 to 40, including or not including bladder's trigone.

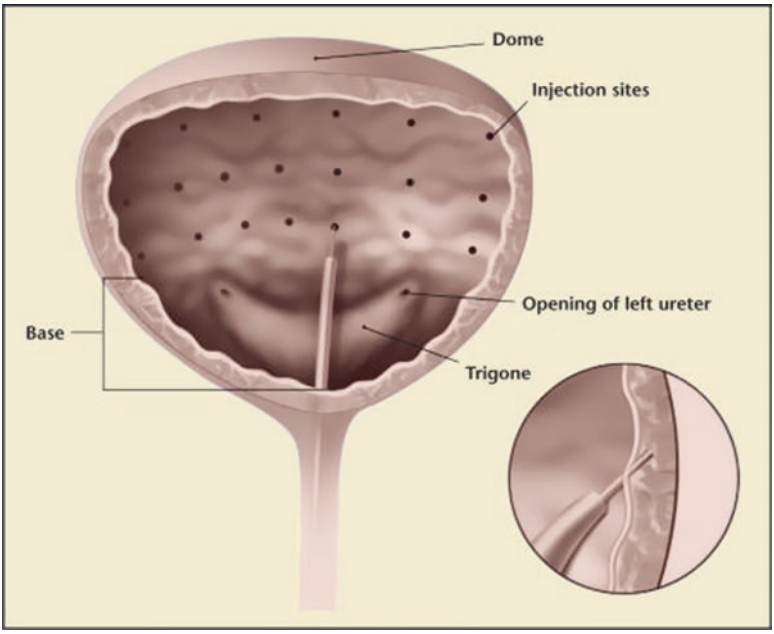

Fig. 7.3 Botox injection of bladder for overactive detruser muscle. From Obstetrics and gynecology 2014. With permission from publisher, Wolter Kluver. Original from Allergan http://www.allergancom/assests/pdf/botox/-pi.pdf

Treatment of Pain with Botulinum Toxins in Multiple Sclerosis

Pain is a common symptom in multiple sclerosis. In one study, 63% of the patients with multiple sclerosis complained of chronic pain [9]. Among several types of pain in MS, three types of pain are most frequent: neuropathic, pain associated with spasticity and tonic spasms.

1-Neuropathic Pain Neuropathic pain has a burning, searing and jabbing quality and the most severe form of it involves the face in multiple sclerosis. Irritation of damaged nerve fibers that provide sensation to the face is believed to be the cause of face pain in MS. The trigeminal nerve, the fifth of 12 nerves that exit the brain, provides sensation of face, inside the mouth, the tongue and the throat. The pain is called trigeminal neuralgia (nerve pain related to the trigeminal nerve). Patients complain of severe bouts of pain lasting for seconds but recurring many times during the day. The most common type of trigeminal neuralgia, however, is seen in older individuals (>50 years of age) without MS due to age related degeneration of this nerve. Trigeminal neuralgia is very rare in young individuals, but can be seen in one out of 300 young patients with multiple sclerosis. Therefore, in a young person, especially when the facial pain affects both sides, the diagnosis of multiple sclerosis should be strongly suspected. Treatment of trigeminal neuralgia is difficult; most patients are not happy with oral medications. High quality studies have shown that injection of Botox and other type A toxin (Chinese type A toxin: Prosigne) with a small and thin needle into skin of the face can alleviate the pain in the common, late onset form of trigeminal neuralgia [11]. No studies are available with botulinum toxins for treatment of TN in multiple sclerosis. However, case reports suggest that injections of botulinum toxin into painful areas of the face is also effective for MS -related trigeminal neuralgia (see below).

How injection of botulinum toxin inside and under the skin can help neuropathic pain has been the subject of many investigations. It is now common knowledge from both animal and human studies that BoNTs not only inhibit the function of acetylcholine (nerve-muscle chemical transmitter) but also diminish the effect of variety of chemicals that are essential for transmission of pain signals from the skin to brain. Though still not approved by FDA (except for chronic migraine), BoNTs injection into and under the skin is now used by many clinicians for a variety of neuropathic pains such as pain associated pain with shingles, pain after limb trauma and so forth based on the published data from high quality studies [10].

Case Report

A 42 year-old women, with history of multiple sclerosis since age 18 with intermittent paralysis, and sensory loss and visual symptoms complained of intermittent severe facial pain. The pain involved the left side of the face and recurred many

timers daily. The episodes of pain were brief (lasting only seconds) but brought tears to her eyes. The pain was described as jabbing and burning. She was treated with several medications including the commonly used drug for trigeminal neuralgia; tegretol and gabapentin that "did not help much". On the scale of 0 to10, most of her pain episodes were described as 9 or 10 in severity. The pain occurred as many as 30 times per day. The MRI of her brain showed no abnormality to explain her facial pain. A neurological examination revealed no motor or sensory deficits. The affected area of the face was injected with Botox in a grid-like pattern, using a small and thin needle. Injections were under the skin, 2.5 units per site at 12 sites (Fig. 7.4). She reported marked pain relief in a week post injection with the pain intensity dropping to 1–3 on a 0–10 scale. Repeated injections every 4 months had the same positive effect. No side effects were reported.

2- Pain Associated with Spasticity As was discussed earlier, stiff muscles of patients with multiple sclerosis are often painful. Muscle pain interferes with rest and sleep and deteriorates the patients' quality of life. In majority of patients with spasticity, botulinum toxin injection into the tight muscles improves muscle pain along with spasticity.

3- Tonic Spasms Tonic spasms are intermittent muscle spasms often affecting wrist and foot, toe and fingers. The result is painful twisting of wrist or feet and flexion of toes or fingers. The cause of these painful spasms in MS is not clear but it is generally attributed to irritation of damaged nerve fibers that travel from brain to muscles. Dr. Restivo and his coworkers found that these spasms improved significantly when Botox, 80–120 units was injected into forearm or leg muscles of five affected patients [12].

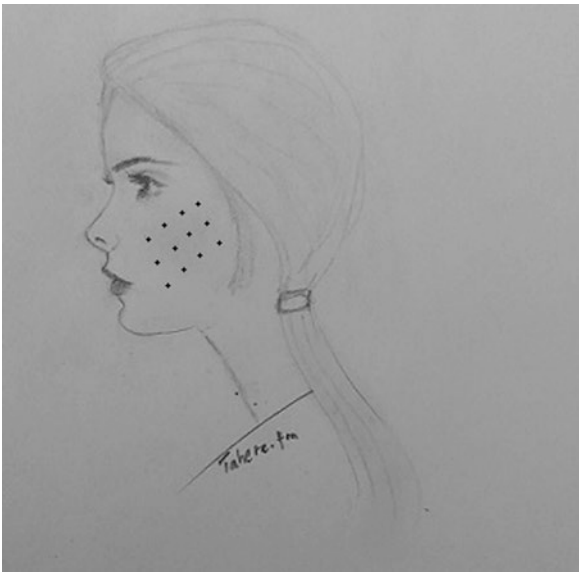

Fig. 7.4 Case report. Sites of Botox injections in a patient with multiple sclerosis and trigeminal neuralgia. Injections are carried out using a thin and short needle and under the skin. Drawing courtesy of Dr. Tahereh Mousavi

Movement Disorders in Multiple Sclerosis

Multiple sclerosis can cause involuntary movements of the muscle due to the disruption of muscle control at the brain level. In general, involuntary movements respond well to injection of BoNTs into the muscle which acts via inhibition of nerve muscle chemical transmitter, acetylcholine (described earlier). Two of these movements are discussed briefly here:

1. Facial myokymia: this is fine twitches of small muscle fibers of the face seen in some patients with multiple sclerosis. It is not painful but a nuisance, esthetically unpleasant and often a cause of social embarrassment. Injection of small amount of Botox 1 to 2 units into the areas of the muscle twitch (barely under the skin of the face) can reduce or stops the movements for 3 to 4 months.
2. Tremor: a special form of tremor, called cerebellar tremor, sometimes, is a disabling symptom in multiple sclerosis. Cerebellar tremor unlike Parkinson tremor increases in amplitude during the hand and forearm motion. Cerebellum (called by some the little brain), is located under Cerebrum, main part of the brain, in the back of the head, and through its extensive connections provides muscle coordination. Multiple sclerosis via disruption of cerebellar connections impairs normal movements and causes a coarse limb tremor. There are some reports that claim injection of Botox into different muscles involved in cerebellar tremor can diminished this high amplitude tremor to a level that is manageable by the patient.

Treatment of Difficulty with Swallowing (Dysphagia)

Muscles of swallowing like other muscles of the body in MS develop increased tone and stiffness as the disease progresses. This stiffness associated with increased muscle reflexes results in difficulty in swallowing. A well- designed study assessed the effects of Botox injection into the muscles of esophagus (the tube connecting the mouth to the stomach) in 14 patients with MS and difficulty in swallowing. Patients were followed carefully at 1,4,6,12,16,18 and 24 months. Difficulty in swallowing improved in all patients following injection of Botox into muscles of the back of the throat which had unusually high tones [13].

Conclusion

Botulinum toxin therapy is useful for several disturbing symptoms of multiple sclerosis. Treatment of tight and stiff muscles (spasticity) and bladder symptoms (inappropriate urge to urinate, leaking and urinary incontinence) are the two most widely used indications which have shown to improve the patients' quality of life. Emerging

data on treatment of face pain and muscle spasms and the swallowing difficulties in MS is also encouraging and expands the utility of BoNT therapy in multiple sclerosis.

References

1. Dilokthornsakul P, Valuck RJ, Nair KV, Corboy JR, Allen RR, Campbell JD. Multiple sclerosis prevalence in the United States commercially insured population. Multiple sclerosis prevalence in the United States commercially insured population. Neurology. 2016;86:1014–21.
2. Zwibel HL, Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care. 2011;17(Suppl 5):S139–45.
3. Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. J Med Econ. 2013;16:639–47.
4. Rizzo MA, Hadjimichael OC, Preingerova J, Vollmer TL. prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler. 2004;10:589–95.
5. Flachenecker P, Henze T, Zettl UK. Spasticity in patients with multiple sclerosis--clinical characteristics, treatment and quality of life. Acta Neurol Scand. 2014;129(3):154–62.
6. Snow BJ, Tsui JK, Bhatt MH, et al. Treatment of spasticity with botulinum toxin: a double-blind study. Ann Neurol. 1990;28:512–5.
7. Mahajan ST, Patel PB, Marrie RA. Under treatment of overactive bladder symptoms in patients with multiple sclerosis: an ancillary analysis of the NARCOMS patient registry. J Urol. 2010;183:1432–7.
8. Ni J, Wang X, Cao N, et al. Is repeat Botulinum Toxin A injection valuable for neurogenic detrusor overactivity-A systematic review and meta-analysis. Neurourol Urodyn. 2017, Jul 26; https://doi.org/10.1002/nau.23354. [Epub ahead of print]
9. Foley PL, Vesterinen HM, Laird BJ, Sena ES, Colvin LA, Chandran S, MacLeod MR, Fallon M. Prevalence and natural history of pain in adults with multiple sclerosis:systematic review and meta-analysis. Pain. 2013;154:632–42.
10. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes -an evidence based review. Toxicon. 2018, January 31; https://doi.org/10.1016/j.toxicon.2018.01.017. pii: S0041-0101(18) 30031-X. [Epub ahead of print]
11. Wu CJ, Lian YJ, Zheng YK, et al. Botulinum toxin type a for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32:443–50.
12. Restivo DA, Tinazzi M, Patti F, et al. Botulinum toxin treatment of painful tonic spasms in multiple sclerosis. Neurology. 2003;61:719–20.
13. Restivo DA, Marchese-Ragona R, Patti F, et al. Botulinum toxin improves dysphagia associated with multiple sclerosis. Eur J Neurol. 2011;18(3):486–90. https://doi.org/10.1111/j.1468-1331.2010.03189.x.

Chapter 8
Botulinum Toxin Treatment of Bladder and Pelvic Disorders

Introduction

Bladder functions through the actin of its muscles. Bladder muscles like any other muscle in the body, respond to nerve signals that come from the brain and spinal cord. Botulinum toxins block the release of neurotransmitters at nerve-muscle junction. Neurotransmitters are chemicals that convey the electrical message of the nerve to the muscle and activate the muscle. In human, the main neurotransmitter of nerve-muscle junction is acetylcholine that activates all skeletal muscles as well as visceral muscles such as those present in the bladder. Clinical research and experience over the past 15 years have proven the efficacy of botulinum toxin injection into the bladder wall in improving bladder overactivity problems. These bladder overactivity problems are either due to damage to the bladder nerves such as seen in spinal cord injury or multiple sclerosis or they may have unknown causes. The former is called neurogenic detrusor overactivity (NDO). Detrusor muscle is the main bladder muscle that participates in bladder filling and emptying. The latter bladder condition is termed simply over active bladder (OAB) or idiopathic (cause unknown) overactive bladder IOB.

Botulinum toxins are also effective in relieving pelvic pain in both genders due to their blocking effect on the pain neurotransmitters. Limited data indicate that pain generated by inflammation of the bladder (interstitial cystitis) also responds to injection of botulinum toxins into the bladder wall.

Botulinum Toxins

Botulinum toxin is produced by a form of bacteria called clostridium botulinum and ingestion of a large amount of the toxins produced by these bacteria leads to the serious illness of botulism. The history of botulinum toxin's discovery as a

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_8

treatment agent when prepared in an injectable and safe form is presented in detail in Chap. 1. There are seven serological types of the toxin (A to G), of which, types A and B are in clinical use due to their long duration of action. Three type A and one type B toxin have been approved by FDA for use in the US. The type A toxins have trade names of Botox, Xeomin and Dysport whereas the trade name for the type B toxin is Myobloc in US, Neurobloc in Europe. The propriety name as well as differences and similarities between these toxins are described in Chap. 3.

Because of the powerful effect of botulinum toxins on nerve- muscle junction (details of the mechanism is described in Chap. 2), over the past 30 years, botulinum toxins have developed as drugs of first line for treatment of several hyperactive movement disorders. Botulinum toxins are now approved by FDA for treatment of blepharospasm (forced and repeated eye closures due to overactivity of eyelid muscles), hemifacial spasm (involuntary spasm of the facial muscles on one side) and cervical dystonia (a hyperactive condition causing neck jerks and abnormal neck postures) [1]. In addition, through the same mode of action (blocking the nerve-muscle junction), botulinum toxins' role has now been established as a major mode of treatment for improving and reducing muscle tone and muscle spasm (spasticity) which occur after stroke or after brain or spinal cord injury [2].

The above mentioned positive results with botulinum toxin therapy in a variety of medical conditions characterized by muscle overactivity have encouraged neurologists and urologists to look into the potential use of botulinum toxins for management of bladder dysfunction related to the overactivity of the bladder's detrusor muscle.

Physiology of Bladder Function and the Role of Detrusor Muscle

In health, human kidneys generate 800 to 2000 milliliters of urine per 24 h. The urine that is generated from the kidneys is carried to the bladder by two tubes called ureters (Fig. 8.1).

The ureters connect the kidneys to the bladder where they insert into the posterior aspect of the lower and narrowed part of the bladder called trigone (Triangle). The drainage of the urine to the outside from the trigone is through a hole that opens into a single tube called urethra. Urethra is short in women 1.5 cm and longer in men (10 cm) since it goes through the length of penis.

The bladder is an ovoid shape structure, located in the lower part of the pelvis. The wider part of the bladder is located on the top, while the narrower part is at the bottom (Fig. 8.2). Storage and emptying of the urine are managed by three essential muscles:

1. Detrusor muscle (Fig. 8.2): This is the main muscle of the bladder wall which while relaxed allows the bladder to expand and store urine; its contraction is essential for the drainage of urine.

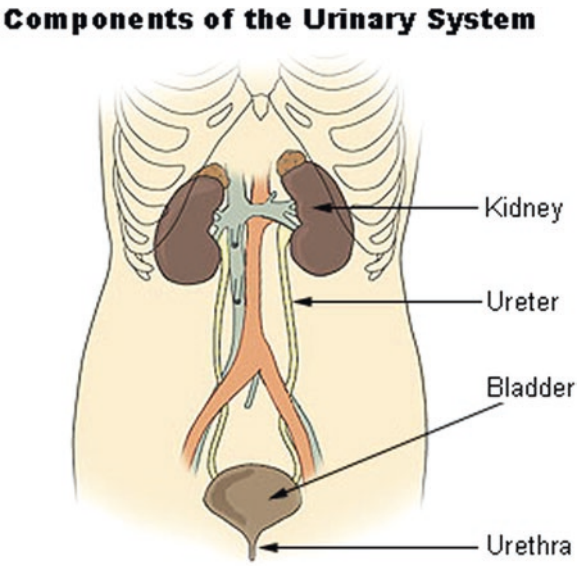

Fig. 8.1 Kidney's, ureters, bladder and urethra. From Wikibooks

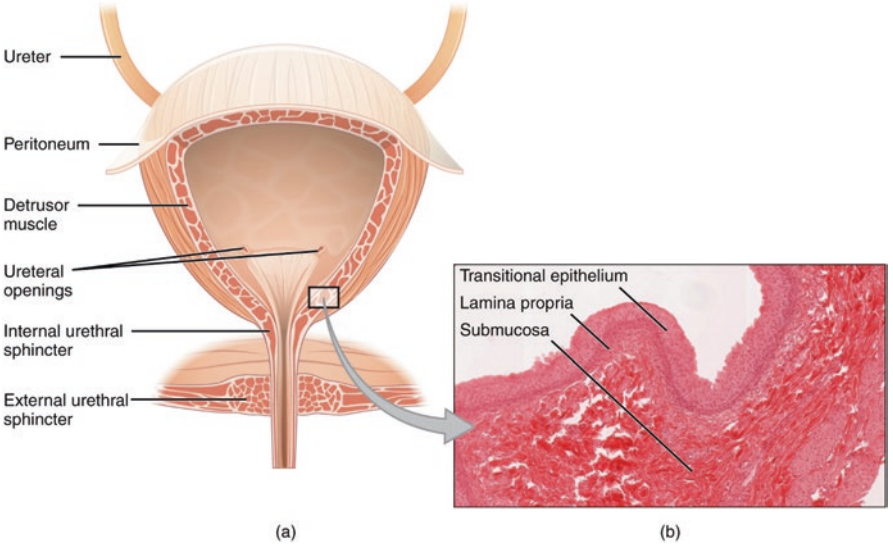

Fig. 8.2 Bladder: base, trigone, detrusor muscle, internal and external sphincters. From https://upload.wikimedia.org/wikipedia/commons/d/dc/2605_The_Bladder.jpg

2. Internal urinary sphincter: This small muscle which is around the neck of the bladder contracts during urine storage and relaxes during micturition letting the urine out of the bladder.
3. External urinary sphincter: this sphincter is located further down on the path of urine drainage, and its function is similar to that of the internal sphincter. However, it is under voluntary control.

The detrusor and internal urinary sphincter are special types of muscles called smooth muscles that are innervated by the autonomic nervous system (sympathetic and parasympathetic), and, hence, are not under voluntary control. The external sphincter, has a structure similar to other muscles of the body referred to as striated muscle and is controlled by volition.

During filling of the bladder, the pressure inside the bladder is constantly sensed by the nerve cells located on the surface of the detrusor muscle. When the bladder pressure reaches a certain point, these nerve cells signal filling of the bladder to the nerve cells located in the spinal cord and brain, which in turn command the release and drainage of urine to bladder muscles. The detrusor muscle contracts and pushes the urine towards the trigone, while the internal sphincter relaxes and lets the urine out toward the external sphincter. At this time, the urgent need for micturition is fulfilled by voluntary relaxation of the external sphincter that pours the urine into the urethra for drainage. The storage and drainage of urine requires proper timing and synergy between detrusor muscle and the two sphincters. In certain neurological conditions, synergy between these muscles does not take place (detrusor -sphincter dyssynergia); this leads to urinary retention. Overactivity or underactivity of detrusor muscles is also the cause of urinary symptoms such as urinary incontinence or retention. Detrusor overactivity is seen in neurological disorders (neurogenic detrusor overactivity -NDO), but sometimes the cause remains undetermined (overactive bladder – OAB). Detrusor underactivity or paralysis of detrusor muscle, occurs in severe spinal cord injury and is not responsive to botulinum toxin therapy.

Neurogenic Detrusor Overactivity (NDO)

Neurogenic detrusor overactivity is the most common type of bladder dysfunction in multiple sclerosis and partial spinal cord injury. Approximately 70% of patients with multiple sclerosis and bladder dysfunction complain of impaired quality of life. Control of bladder function takes place at several levels in the central nervous system: spinal cord, lower part of the brain (brain stem- Pons) and cortex of the brain where the large nerve cells are located. Multiple sclerosis and spinal cord injury damage the nerve cells and nerve fibers that control bladder function. The result of this damage is increased excitability of the fibers that descend from the brain to the bladder and provide nerve supply of the detrusor muscle. This is similar to what happens to other muscles of the body that become overactive in these two conditions whereby patients demonstrate increased reflexes. The term reflex bladder is also used sometimes to characterize overactivity of the bladder's detrusor muscle in NDO.

The symptoms of NDO consist of urinary urgency, urinary frequency and inability to hold urine (incontinence), caused by involuntary and abnormal contractions of a hyperactive detrusor muscle. Urinary urgency (desire to urinate) is the most common symptom and half of the people with urinary urgency have- urge incontinence-wetting themselves during the urge to urinate.

Neurogenic detrusor overactivity often leads to decreased bladder capacity and to residual urine with incomplete bladder emptying. Many patients experience discomfort at the time of urination. These symptoms make the patient prone to developing recurrent bladder infections. Furthermore, increased detrusor pressure can cause backing of urine, dilation of ureters (hydronephrosis) resulting to subsequent damage to the kidneys.

Conventional treatments of neurogenic detrusor overactivity include bladder training, pelvic floor exercises and medications. Among general measures, losing weight in overweight patients and avoiding drinking excessive tea or coffee are often recommended. Bladder training is usually a 3–12- week course that includes different behavioral approaches such trying to delay voiding to void when feeling urge to urinate. Patient starts with 5–10 min deferral, gradually extends delaying time to several hours. This may not be successful in some patients since it requires the ability to tighten the pelvic floor. Scheduling regular voiding times even in the absence of urge to void is also a part of bladder training. Pelvic floor exercises aim to strengthen muscles of the pelvic floor which are located in the proximity or are attached to the bladder (Fig. 8.3). The most common exercise is known as kegel exercise, usually taught to the patient by the physician or a physical therapist. It may take up to 8 weeks before giving any results.

Medical therapy is focused on "urge incontinence" which is the most disturbing symptom. The drugs that are used for treatment of urge incontinence are usually in

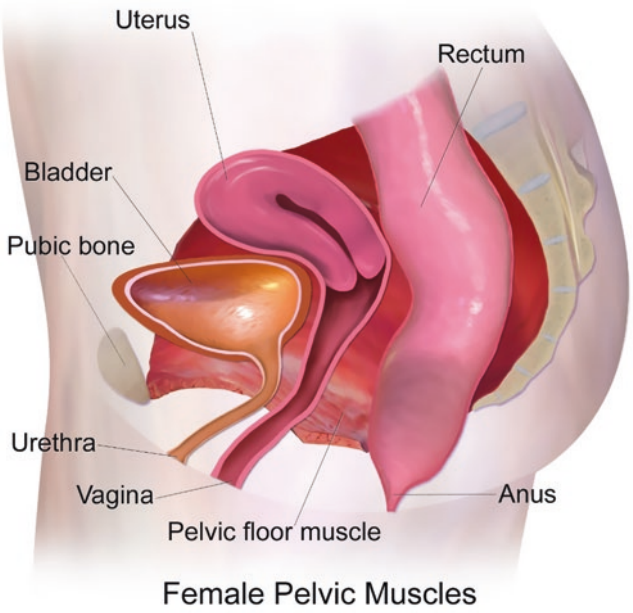

Fig. 8.3 Position of the bladder and pelvic floor muscles- From Wikimedia commons licensed under creative commons attribution

the category of anticholinergics since they block the action of acetylcholine- the previously mentioned neurotransmitter that activates muscles after receiving the nerve signal. Several drugs of this category are available in the market under different trade names such as Detrol and Ditropan. Dryness of the mouth, dryness of the eyes and constipation are common side effects. Elderly patients may experience impairment of memory and confusion. Unfortunately, long-term effects of medications in treatment of overactive bladder related to nerve damage is disappointing. Research have shown that within 2 years after initiating the treatment, half of the patients stop taking these medications either due to inefficacy or due to undesirable side effects [3].

Botulinum Toxin Treatment of NDO

In 2000, Schurch and his colleagues first demonstrated the effectiveness of Botox injections into the bladder wall in patients with detrusor muscle overactivity. Seventeen of their 19 patients completely regained urinary continence 6 weeks after treatment and, in 11 patients, continence of urine persisted for 36 weeks after a single session of injections. Furthermore, they have shown that patients' maximum bladder capacity increased up to 482 milliliters.

In 2010, FDA approved Botox injections into the bladder wall for management of NDO symptoms based on two large multicenter and double- blind studies (both doctor and patients unaware of the type of injection, toxin or placebo) consisting of 217 and 416 patients affected by multiple sclerosis and/or spinal cord injury. These carefully crafted studies which also compared the effect of 200 units of Botox with 300 units, demonstrated significant reduction of incontinence episodes after Botox injections as well as marked improvement of patients' quality of life as measured by standard quality of life rating scales [4–6]. Furthermore, Botox injections were safe and no patient developed any serious side effects. As 200 units was as effective and had less side effects compared to the 300 units, the FDA approval was issued for the 200 unit dose. Subsequently, several follow up studies have demonstrated maintenance of efficacy after repeated injections of Botox over years (3–6 years) with the time interval between injections varying from 7 to 11 months.

The main side effect of Botox treatment of neurogenic detrusor overactivity is urinary retention observed in 9% of the treated patients which will require daily self-catheterization. For many patients with spinal cord injury or multiple sclerosis, this may not be a major issue since they are already in that stage. The need for self-catheterization after Botox injections, however, decreases with the passage of time. A recent follow up study of 227 patients with NDO have shown that the need for self-catherization in the third and fourth year after initiation of Botox therapy dropped to 8% and 0% respectively [7]. Increased urinary tract infections were noted after Botox injections in patients with multiple sclerosis, but not among patients with spinal cord injury.

Injection Technique

For injections, 100 units of Botox are diluted in 10 cc of normal saline and injected via an endoscope into the bladder. An endoscope is a device which can visualize the bladder wall and maneuvered inside the bladder. Injections are superficial and on the surface of the detrusor muscle at multiple sites almost in a grid-like pattern**.** The initial FDA approved protocol spares the trigone of the bladder and recommends a total dose of 200 units of Botox (Fig. 8.4).

In recent years, several authors have recommend including the trigone of the bladder in the injected area since this region of the bladder is rich in nerve fibers; in the experience some investigators inclusion of the trigone in the plan of injection provides better outcome. Dr.Smith and his colleagues from Baylor College of Medicine in Houston, Texas include the trigone and adjust the dose based on the type and severity of the bladder dysfunction. Their protocol for patients with mild symptoms recommends 9 to 10 injection sites with a total Botox dose of 100 units. For patients with severe symptoms who are already catheterizing themselves, 30–40 injection sites are recommended with a total Botox dose of 200 units (Fig. 8.5).

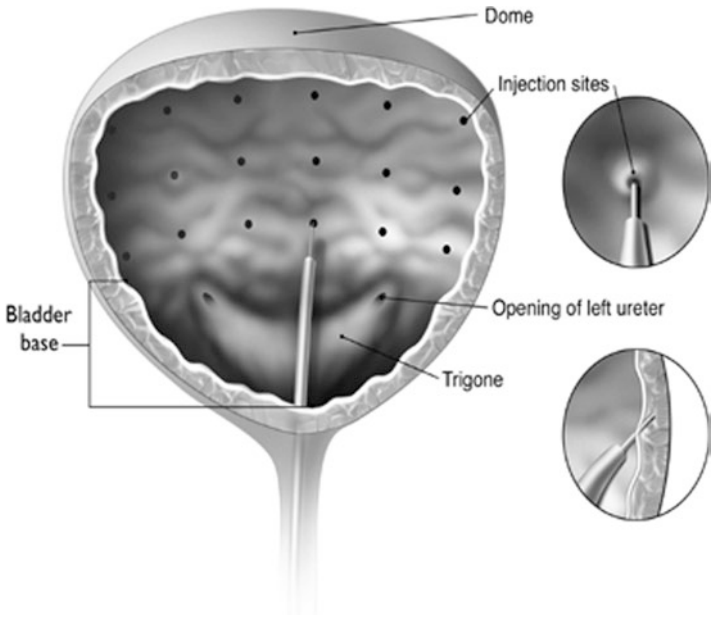

Fig. 8.4 Site of Botox injections for overactive bladder sparing the trigone. From Talab et al. Botulinum Toxin Treatment in Clinical Medicine. Jabbari B(Editor). Printed with permission from Springer

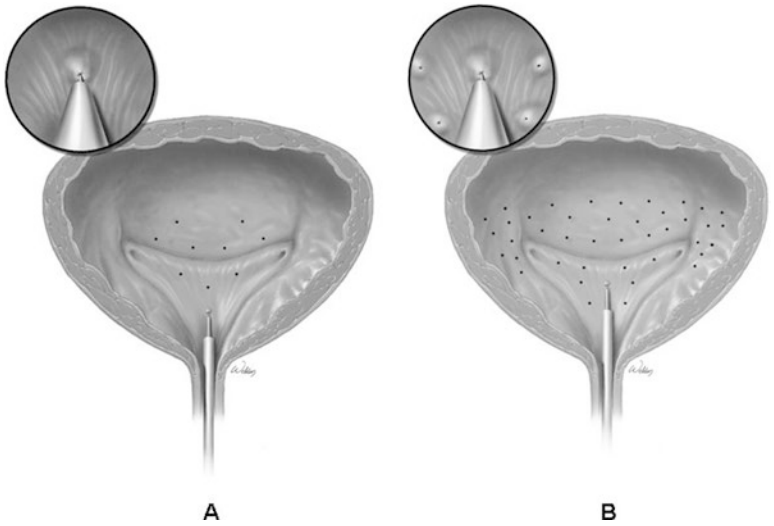

Fig. 8.5 Technique of bladder injection. (**a**) for patients with mild symptoms (**b**) for patients with severe symptoms. From Smith and Chancellor. Seminars of Neurology 2016. With permission from publisher-Thieme

Overactive Bladder of Unknown Cause (OAB)

This category includes patients with undetermined cause of bladder overactivity. Among adults a prevalence of up to 16.9% has been reported in general population increasing to 30% among those of 75 years or older [8]. The symptoms of OAB are very similar to those of NDO; mainly urinary urgency, frequency and incontinence. These symptoms are managed similarly with bladder training, pelvic floor exercise and anticholinergic medication. Myrbetrig is a newer drug in the market that enhances the effect of adrenergic (adrenaline enhancing) system and can alleviate some of the symptoms of OAB. Its side effects consist of allergic reactions, nausea and headaches as well as raising the blood pressure. Like NDO, failure of medical therapy is not uncommon in OAB. Also, the side effects of medications, especially among the elderly of which memory loss and confusion are the most disturbing, limit proper dosing.

In 2003, Dykstra and his colleagues were first to show that injection of botulinum toxin B (Myobloc) into the bladder wall can reduce the urinary frequency and incontinence of patients with OAB (for descriptions of different types of botulinum toxins and their units see Chap. 3). The authors compared the effect of different doses of myobloc starting with 2500, 5000,10,000 and up to 15,000 units which roughly approximate 50 to 250 units of Botox. They found no difference in efficacy between different doses. Subsequently several carefully designed, high quality, double blind studies with Botox in large number of patients confirmed the efficacy of

Botox for management of OAB symptoms. Botox was approved by FDA for treatment of overactive bladder in 2013. The technique of injection is similar to what was described earlier for overactive bladder due to nervous system damage, neurogenic detrusor overactivity (NDO).

Cost Effectiveness

Several studies have shown that despite high cost of Botox therapy, this treatment is cost effective for management of NDO and OAB symptoms. It is used infrequenty, every 6–9 months-has fewer side effects and, in many instances, eliminates the need for taking oral medications. Successful Botox therapy of NDO or OAB leads to reduced number of doctor's office and emergency room visits and less hospitalizations [9].

Prostate and Bladder Dysfunction

Among male patients increased sized of prostate (prostatic hypertrophy) exerts pressure against urethra (the tube draining urine from the bladder) – and causes a variety of symptoms including slowness of voiding, weak urine stream, incomplete emptying and sometimes incontinence. Researchers have tried to show if injection of botulinum toxin into prostate by decreasing the size of prostate can help the urinary problems. The results of research in this area is conflicting. Currently, botulinum toxin therapy (injections) is not recommended for management of urinary symptoms related to enlarged prostate.

Improper Contraction of External Sphincter of the Bladder at the Time of Expected Relaxation

This condition is medically named sphincter-detrusor dyssynergia (SDD) meaning loss of synergy between these two muscles. As was mentioned earlier, when bladder muscle contacts in response the nerve signal, external sphincter muscle (Fig. 8.2) relaxes and lets the urine out of the bladder. In SDD, external sphincter contracts instead of relaxation in response to detrusor contraction. SDD is caused by medical disorders that damage the nerve fibers that control bladder function; these nerve fibers originate from nerve cells of the brain and spinal cord. Disease conditions such as spinal cord trauma, stroke or multiple sclerosis are common cause of DSD. The result of impaired bladder emptying is urine retention, recurrent infections and potential damage to the kidneys.

The technique of injection is well described. Injections can be done by a cystostope which in men is inserted through the penis. After reaching external sphincter, injections are usually performed at 4 points (3, 6, 9 and 12 o'clock locations). Among women, because of the short length of urethra, external sphincter is closer to the surface.

Although many small studies have shown efficacy of Botox in relieving the symptoms of DSD (lasting 3–9 months), better quality and larger studies have not produced convincing results. At the present time, Botox treatment of DDS is not FDA approved but it is performed in some centers off label, by experienced physicians. The main side effect of this treatment is urinary incontinence which results from unwanted degree of weakening of the external sphincter muscle.

Botulinum Toxin Indications in Urogenital Pain Syndromes

As mentioned earlier, injection of US marketed botulinum toxins (Botox, Xeomin, Dysport and Myobloc) into the muscle, not only inhibits the release of acetylcholine in nerve-muscle junction (a neurotransmitter that activates muscle after receiving nerve signal), but also reduces and inhibit the function of a number of pain neurotransmitters. These agents help to convey pain sensation from periphery to the brain. Because of this action, researchers began to explore the effect of botulinum toxin therapy on urogenital pain syndromes. There is now supporting evidence that, at least in three of these conditions, local injection of botulinum toxins alleviates pain. These three conditions consist of male pelvic pain, female pelvic pain and local pain related to chronic bladder infection (interstitial cystitis).

1. Male Pelvic Pain: Male pelvic pain is usually the result of chronic inflammation or infection of prostate (chronic prostatitis). This condition is classified by the National Institute of Health (NIH) as chronic prostatitis/chronic pelvic pain syndrome. It is the most common urological disorder among men under the age of 50 with a prevalence 2.5–16%. The pain is felt in the lower part of the abdomen, pelvis and genitalia and impairs the quality of life by its severity and persistence.

The efficacy of botulinum toxin therapy for male pelvic pain is supported by publication of two high quality studies. Both studies used Botox but the technique of injection was different. In the smaller study which comprised 13 patients, the injection was directed into one of the muscles of the pelvic floor (bulbospongiosus), whereas in the larger study (60 patients), the site of injections was the lateral lobes of prostate (at 3 locations). Both studies used Botox with comparable doses of 100 to 200 units. Investigators of both studies reported that patients described a marked reduction in severity and frequency of pain at 1, 3 and 6 months after injection' concurrent with notable improvements of their quality of life [10, 11]. Using the criteria of the Development Guidelines subcommittee of the American Academy of Neurology (AAN) (see Chap. 3), botulinum toxin therapy for male pelvic pain

would have a level B efficacy (probably effective – one class I study). For this indication, however, Botox does not have FDA approval. The treatment of male pelvic pain with botulinum toxin is hence, off label, based on the currently available supporting literature.

2. Female Pelvic Pain: Chronic pelvic pain among women is most often (71–87%) associated with a medical condition called endometriosis [12]. In endometriosis, a tissue identical to the lining of the uterine cavity (endometrium) is found abnormally in other pelvic organs including the ovaries and the tubes that connect ovaries to uterus. This abnormally located and misplaced issue, increases in size and bleeds just as the normal endometrium does during the menstrual cycle.

The pelvic floor contains a dozen small muscles that surround the rectum and vagina and connect the bony structures of front and back of the pelvis (pubis and tail bones). Abbott and his coworkers from Australia were the first to show that injecting Botox into two of the pelvic floor muscles (one connecting pubis to rectum and one connecting pubis to tailbone) relieves pelvic pain in a group of women, a majority of whom had endometriosis. Their study consisted of sixty women, 30 of whom received 80 units of Botox and 30 received placebo (normal saline) [13]. The patients were followed at 4-week intervals for 26 weeks. In addition to relief of pelvic pain, women who received Botox, reported having less pain during intercourse (dyspareunia) compared to those who received saline. Dr.Abbott and his colleagues observation, was supported by several other observations, among them a recent study that reported pain relief and improvement of quality of life following Botox injection in women with pelvic pain who were followed 6 months [14]. Close to 5% of the patients reported transient urinary and fecal incontinence as side effects of Botox injections. Currently, Dr.Barbara Karp and her colleagues at the National Institutes of Health are investigating the effects of botulinum toxin injections in women with pelvic pain and endometriosis. The preliminary results of this carefully crafted study are encouraging; the full results will be available, hopefully, over the next few months.

3. Pain related to chronic bladder infection (interstitial cystitis, bladder pain syndrome): Bladder pain syndrome is a debilitating condition that affects millions of people worldwide. It is believed to be due to chronic inflammation of the internal bladder lining (in contact with urine) that leads to irritation, pain in the area of the bladder, urinary frequency and urinary urgency. Failure of body's immune system is suspected in some patients but the cause of this bladder problem is generally unknown. No effective treatment is currently available. Instillation of hyaluronic acid into bladder helps some patients and reduces the irritation of the bladder lining, but the results are often temporary and pain recurrence is common. Pain killers offer only modest pain relief in bladder pain syndrome. In recent years, several, carefully designed studies have shown that injection of bladder wall with botulinum toxins can relieve pain and other symptoms of bladder pain syndrome. The most recent of these high- quality studies, found that both injection of the body of bladder and bladder trigone relieved bladder pain in

about 50% of the patients, a considerably higher rate of success compared to that achieved by the placebo (saline) injection [15]. Although Botox injections of the bladder are not yet approved by FDA for treatment of bladder pain syndrome, the American Urological Association recommends it as the fourth mode of treatment for this indication based on the currently available literature.

Conclusion

Botulinum toxin injection into bladder wall improves symptoms related to bladder dysfunction and discomfort (urgency, frequency). Botulinum toxin therapy is approved by FDA for treatment of bladder overactivity either related to nerve damage (neurogenic detrusor overactivity-NDO) or bladder overactivity of undetermined cause (overactive bladder-OAB). FDA has not approved botulinum toxin therapy for other bladder disorders, but the existing literature supports its efficacy in male and female pelvic pain syndrome and in pain related to chronic bladder inflammation (bladder pain syndrome). Other potential areas of botulinum toxin treatment utility in the field of bladder dysfunction or pelvic pain such as pelvic pain related to enlarged prostate, bladder dysfunction due to lack of synergy between bladder's detrusor muscle bladder and bladder's sphincter are also being currently explored.

References

1. Jankovic J. An update on new and unique uses of botulinum toxin in movement disorders. Toxicon. 2017 Sep 6; https://doi.org/10.1016/j.toxicon.2017.09.003. pii: S0041-0101(17)30276-3 [Epub ahead of print]
2. Kaku M, Simpson DM. Spotlight on botulinum toxin and its potential in the treatment of stroke-related spasticity. Drug Des Devel Ther. 2016;10:1085–99.
3. Chancellor MB, Yehoshua A, Waweru C. Limitations of anticholinergic cycling in patients with overactive bladder (OAB) with urinary incontinence (UI): results from the CONsequences of Treatment Refractory Overactive bladder (CONTROL) study. Int Urol Nephrol. 2016;48:1029–36.
4. Ginsberg D, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol. 2012;187:2131–9.
5. Cruz F, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011;60:742–50.
6. Nitti VW, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol. 2013;189:2186–93.
7. Kennelly M, Dmochowski R, Schulte-Baukloh H, et al. Efficacy and safety of onabotulinumtoxinA therapy are sustained over 4 years of treatment in patients with neurogenic detrusor overactivity: final results of a long-term extension study. Neurourol Urodyn. 2017;36:368–75.
8. Abrams P. Describing bladder storage function: Overactive bladder syndrome and detrusor overactivity. Urology. 2003;62(supplement 2):26–37.

9. Carlson JJ, Hansen RN, Dmochowski RR, et al. Estimating the cost-effectiveness of onabotulinumtoxinA for neurogenic detrusor overactivity in the United States. Clin Ther. 2013;35:414–24.
10. Gottsch HP, Yang CC, Berger RE. A pilot study of botulinum toxin A for male chronic pelvic pain syndrome. Scand J Urol Nephrol. 2011;45:72–6.
11. Falahatkar S, Shahab E, Gholamjani Moghaddam K, Kazemnezhad E. Transurethral intraprostatic injection of botulinum neurotoxin type A for the treatment of chronic prostatitis/chronic pelvic pain syndrome: results of a prospective pilot, double-blind and randomized, placebo-controlled study. BJU Int. 2015;116:641–9.
12. Aredo JV, Heyrana KJ, Karp BI, et al. Relating chronic pelvic pain and endometriosis to signs of sensitization and myofascial pain and dysfunction. Semin Reprod Med. 2017;35:88–9.
13. Abbott JA, Jarvis SK, Lyons SD, Thomson A, Vancaille TG. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol. 2006;108:915–23.
14. Morrissey D, El-Khawand D, Ginzburg N, et al. Botulinum toxin A injections into pelvic floor muscles under electromyographic guidance for women with refractory high-tone pelvic floor dysfunction: a 6-month prospective pilot study. Female Pelvic Med Reconstr Surg. 2015;21:277–82.
15. Jiang YH, Jhang JF, Lee CL, et al. Comparative study of efficacy and safety between bladder body and trigonalintravesical onabotulinumtoxina injection in the treatment of interstitial cystitis refractory to conventional treatment-A prospective, randomized, clinical trial. Neurourol Urodyn. 2018, January 13; https://doi.org/10.1002/nau.23475. [Epub ahead of print]

Chapter 9
Botulinum Toxin Therapy for Problems Related to the Gastrointestinal System (Alimentary Tract)

Introduction

Alimentary tract includes mouth, throat, esophagus (the tube that connects the throat to the stomach), stomach and the intestines(gut). Food moves through the alimentary tract and is digested in the stomach and further digested and absorbed in the gut. The alimentary tract (AT) has a muscular wall. Two types of muscles are represented in the AT, striated and smooth muscles. Striated muscles, like those of arm, leg and trunk muscles can be moved at will, whereas smooth muscles' function is not controlled by volition. Most muscles are of the stomach, gut or bladder are of the smooth type; the individual is not usually conscious of their movement.

In the alimentary system, from upper part of the esophagus (the tube that connects the mouth to stomach) to its end (anus, the orifice that through which solid refuse is excreted), there are five strong circular muscles. These circular muscles are called sphincters. Sphincter is a ring shaped muscle that encircles an opening or a passage in the body. In disease conditions, spasm or unwanted contraction of these sphincters can cause pain and discomfort and interfere with the passage of food. The first sphincter of AT is located in the upper esophagus (upper esophageal sphincter -UES) just below the lower end of the throat (pharynx) (Fig. 9.1). This sphincter relaxes during swallowing (initiated by contraction of throat muscles) letting food enter into the esophagus.

The second sphincter is located at the junction of the esophagus and stomach (lower esophageal sphincter- LES). Contraction of this sphincter closes the opening between esophagus and stomach when no food is consumed. During food consumption, and after contraction of the UES, the LES relaxes, opens and lets the food enter into the stomach.

The third sphincter is between the stomach and the small intestine. This sphincter is called pylorus. Pylorus in Greek means gate keeper. From this small circular opening partially digested food passes to the duodenum (first part of small intestine).

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_9

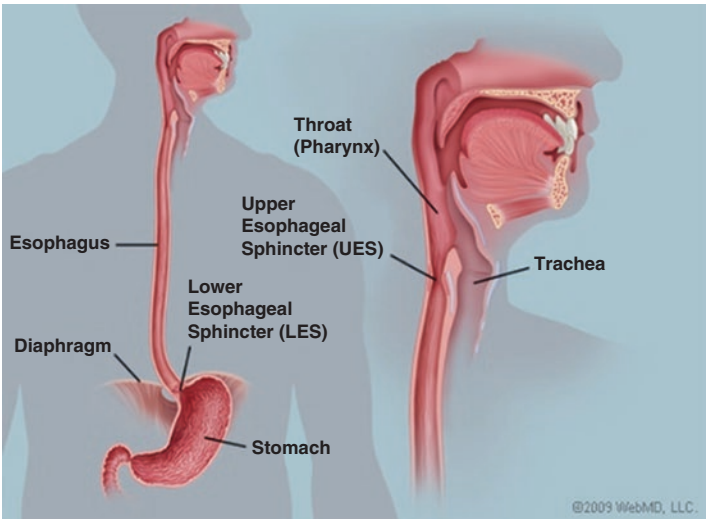

Fig. 9.1 Anatomy of the throat, the esophagus and the two esophageal sphincters -From Mathew Hoffman M.D. Human Anatomy-Digestive disorders- picture of Esophagus – 2009 and 2014 LLC with permission from Web Med

The fourth sphincter controls the opening and closing of the bile duct. Bile which is important for food digestion and is produced in the gall bladder enters the gut through the bile duct. The sphincter that controls the opening and closing of the bile duct is called sphincter of Oddi, named after an Italian physician who first described it (Fig. 9.2).

The fifth sphincter- the anal sphincter -encircles the anus and controls the act of defecation. Relaxation of this sphincter lets the food refuse out of the body.

All these sphincters can be affected and may not function properly if the brain or spinal cord is damaged and the sphincters' nerve supply from central nervous system is interrupted. Common causes of such damages are stroke, trauma, Parkinson's disease and multiple sclerosis. Brain and spinal cord control the function of alimentary sphincters through fine motor fibers. In normal conditions, the function of every muscle in the body (including alimentary sphincters) is maintained through a balance between excitation and inhibition. Brain excites the muscles through excitatory fibers that induce muscle contraction. These fibers release a chemical at their end that excites the muscle; this chemical (transmitter) is called acetylcholine. The inhibitory fibers also have their own transmitter which is different from acetylcholine. For reasons that are not well understood, conditions that commonly damage the brain or spinal cord, damage the inhibitory fibers more often than the excitatory fibers. This tilts the balance towards excitation that gradually keeps the muscles in a state of continuous tightening and contraction. In the limb muscles, this increased muscle tone is called spasticity. The same tightening that affects the limb muscles can affect the function of all 5 above mentioned sphincters of the alimentary tract. Therefore, tight sphincters can interfere with the function of alimentary system at

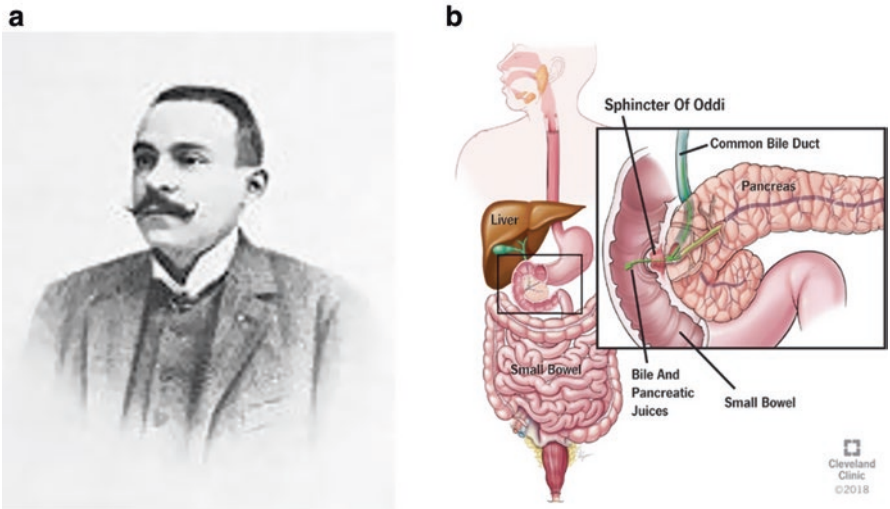

Fig. 9.2 (**a**) Ruggero Oddi, the Italian anatomist that described the bile duct sphincter (**b**) Sphincter of Oddi through which bile and pancreatic ducts gain access to small intestine. Reproduced with permission from Cleveland Clinic

different levels. Botulinum toxin injection into any muscle (striated or smooth) can block the release of acetylcholine from the nerve endings and results in muscle relaxation. Because of this function, injection of BoNTs into the hyperactive muscles has now become a major (and in many cases the first line of treatment) in conditions that cause involuntary muscle movements [1]. This is the basis of using botulinum toxin therapy for treatment of alimentary symptoms related to hyperactive sphincter disorders.

Upper Esophageal Sphincter (UES)

UES is located in the lower end of the throat (pharynx) and is vertically 1 to 1.5 inches long (Fig. 9.1). Its main function is to prevent air from the lungs getting into the throat and prevent food coming back from the esophagus into the throat (reflux) after swallowing. After the initiation of swallowing, UES relaxes and lets the food pass from the throat into the esophagus. The act of swallowing generates a wave of muscle contractions in the esophagus downward that moves the swallowed food or liquid toward the stomach. The medical term for these wave- like contractions of esophageal muscles is peristaltis, a term that also applies to the regular movements of the stomach and gut muscles mixing and moving the food through the alimentary system. A tight UES caused by brain damage is unable to function properly. Patients complain of throat tightness, difficulty swallowing, food getting stuck in their throat. When the food is forced down, it may inaccurately move into the windpipe causing strong coughs.

Treatment of UES tightness includes swallowing exercises, administration of medications and surgery. A large number of swallowing exercises are prescribed by speech therapists for management of UES tightness. These include forced multidirectional tongue movements, jaw opening and closing exercises, and stimulation of the palate with ice-cold spoons. In Shaker exercise, the patient lays flat on the back without a pillow and lifts the head while looking at the toes for 10–15 sec; this exercise is repeated 5–6 times during the day. Other exercises include performing a hard swallow several times a day. In Mendelsohn Maneuver, the individual keeps two fingers against his/her Adam's apple(A'A) and then swallows. The Adam's apple (the frontal protruded cartilage of the neck) moves up during wallowing and comes down after swallowing is over. Patient is instructed to push gently against it and prevent the A'A from coming down after swallowing for a few seconds. This is repeated several times a day.

Medications are not effective in relieving swallowing problems related to the tightness of UES. Balloon dilatation of the constricted sphincter is effective, but the effects are transient. Several surgical procedures have been practiced for improving swallowing problems in this condition. Cutting some of the muscle fibers of this sphincter by surgery offers partial relief, but the procedure has the risk of infection and voice impairment; the latter due to damage to the nerve for the upper part of the windpipe. Endoscopic laser surgery (using a device that visualizes the area), offers a safer approach with fewer side effects.

Botulinum Toxin Treatment of UES Dysfunction

Based on the known effect of botulinum toxins on nerve-muscle junction, i.e. inhibition of the excitatory transmitter acetylcholine, investigators began to look at the effects of injection of BoNT into UES for relief of UES tightness.

The first report on efficacy of Botox in relieving tightness of UES was published in 1994 [2]. The authors injected a total of 20 units of Botox into the cricopharyngeal muscle, a muscle that connects the Adam's apple cartilage in front of the neck to the lower throat muscles and to LES. Five of seven patients had complete relief of symptoms after injection. Dr.Sharzehi and his co-workers review of 2016 covered 200 reported patients with LES tightness in whom the success rate with botulinum toxin injection ranged from 43 to100% [3].

In 2017, Dr. Alfonso and his colleagues published the largest patient series of UES dysfunction treated with BoNT injections [4]. Sixty seven patients with UES dysfunction, were injected with 15–20 units of Xeomin (a BoNT type A with units comparable to Botox)) into the cricophryngeal muscle. The causes of UES in these patients included stroke, trauma and multiple sclerosis. The authors described 52% of the patients as high responders since BoNT injection into the region of LES resulted in >2 levels of improvement in dysphagia outcome severity scale (DOSS). In 67% of the patients, the positive effect of BoNT injection lasted more than 4 months; some of these patients had relief that lasted up to one year. No serious

side effects were noted in the responders. However, two patients who did not initially respond and were reinjected developed pneumonia. The authors emphasized risks associated with reinjection of non-responders. Others reported that swallowing may get worse for a few days following BoNT injection before a sustained satisfactory response that often lasts for months becomes apparent.

Currently, some ear-nose and throat specialists in the US and abroad use botulinum toxin injections into the UES sphincter area for treatment of the associated swallowing problem. The 52% rate of success quoted in the most recent review is substantial if one considers poor response to oral medications and the fact that many patients may not be keen about having surgical intervention. The procedure, however, needs to be done by someone experienced with botulinum toxin injections and one who knows well the anatomy of the throat region.

Tightness of Lower Esophageal Sphincter (LES)– Achalasia

The word achalasia which is of Greek origin means failure to relax (Khalan, Khalasis: relaxing). This entity was first described by an English physician, Thomas Willis, in 1673.

In this condition, LES (Fig. 9.1) fails to relax and allow the passage of food from esophagus to the stomach. Unlike dysfunction of UES which often occurs during the course of well- known neurological problems (stroke, trauma, Parkinson), in most cases of LES dysfunction (achalasia), the cause is unknown. It is now generally believed that achalasia is a neurological disorder due to the failure of nerve cells located in the lower part of the brain (brain stem) that are responsible for both relaxation of the LES and peristalsis of the esophagus. Peristaltic movements of the esophagus push the swallowed food downward toward LES. Loss of relaxation of LES and peristaltic movements of the esophagus leads to a large, dilated esophagus which contains copious saliva and undigested food. This can be easily visualized by radiography following swallowing a large volume of barium. The test will show stagnant barium column in a dilated esophagus and a very narrow and bird-beak shape LES at the junction of the esophagus and stomach (Fig. 9.3). Fluoroscopy (video) of the esophagus can show the absence of peristalsis, the wave like movements that move the food down the esophagus toward the lower esophageal sphincter.

Achalasia is rare and has an incidence of 0. 5–1.63 in 100,000 individuals. The symptoms start slowly with most patients seeking medical attention years after the onset of symptoms (average 4–6 years). The most frequent symptom is difficulty in swallowing which is more prominent for solid food than liquids. Heart burn and regurgitation of food are the next two common symptoms. Smaller percentage of the patients (30–40%) complain of weight loss and chest pain. As the disease progresses difficulty in swallowing becomes a disabling symptom.

The aim of treatment in achalasia is to reduce the tone and tightness of the lower esophageal sphincter. To achieve this goal, two approaches are commonly

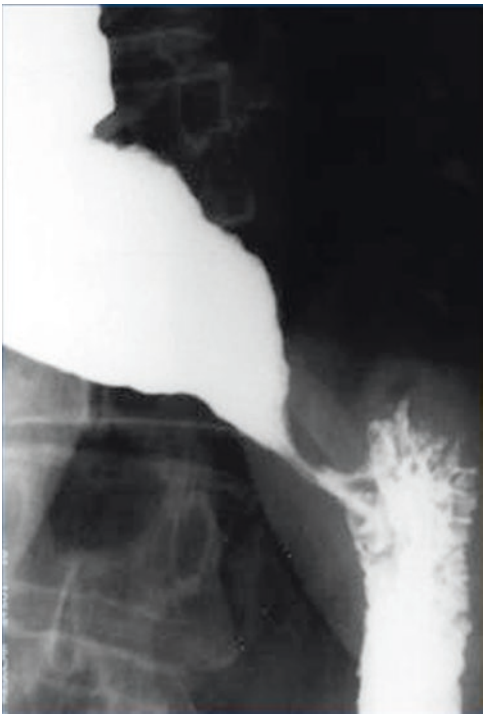

Fig. 9.3 Barium swallow test in achalasia showing a bird- beak shaped LES between a dilated esophagus on the left and the stomach (lower right). Form Sharzehi and schey 2018 – Printed with permission from Springer Publisher

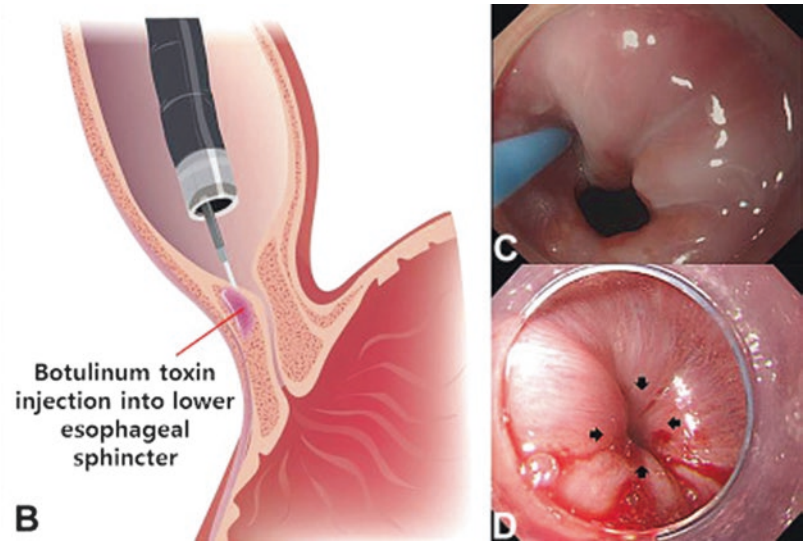

Fig. 9.4 The technique of BoNT injection of lower esophageal sphincter (LES) in achalasia. The needle which is attached to an endoscope, injects the Botox into the contracted LES at the junction of esophagus and stomach. D- shows injection sites into LES into 4 quadrants. From Shim 2014 . Reproduced with permission from Elsevier

implemented. The area of narrowing can be dilated via a procedure called pneumatic (balloon) approach. Alternatively, some of the fibers of the lower esophageal sphincter can be cut (myotomy) through a surgical approach. Although initial success rate is high (85% for dilation and 90% for myotomy), a substantial number of patients demonstrate recurrence of symptoms after 4–6 years.

Medical treatment of achalasia is not very effective. Calcium channel blockers and nitrates have been prescribed with very modest results. It is this medical and surgical treatment restrictions in achalasia that welcomes a new mode of treatment which provides efficacy and has a reasonable safety profile.

Botulinum Toxin Treatment of Achalasia

The first high quality study investigating the efficacy of BoNT injection into LES in achalasia was published by Dr. Pasricha and co-workers in 1995. These investigators have shown that injection of Botox into LES markedly reduces the sphincter pressure, relaxes it and improves the patient's symptoms. The findings were highly statistically significant when compared to the placebo (salt water) injections. Six months after BoNT injection, 14 of 21 patients were still in remission. Botox was injected into LES using endoscopy,a device that inserted into the mouth, moved through the throat and directed to lower esophagus. Four injections, each 20 units, were used covering all four quadrants of the esophagus.

No serious side effects were noted. Other investigators have reported a transient over-relaxation of LES after BoNT injection as a side effect resulting in reflux and heart burn. Although high quality studies of BoNT therapy in achalasia have described no serious side effects, the procedure has a potential of causing serious complications due to the proximity of the injecting needle to vital organs. A single case of death has been reported caused by ruptured lung during LES injection.

The success rate of Botulinum toxin injections into LES in achalasia has been found to be comparable with balloon dilatation and surgery (over 80%). Botulinum toxin injections are believed to have less side effects compared to surgery. Reinjection after 6–12 months is required. Recent studies have shown that two types of botulinum toxin A, Botox and Dysport (see Chap. 5 for toxin types), are equally effective in improving the symptoms of achalasia.

Sphincter of Oddi (SO) Dysfunction

As described earlier, this is another sphincter that is important in proper progression of alimentation. This circular muscle controls an opening through which both bile and enzymes from the pancreas enter the gut, both important players in food digestion (Fig. 9.2). Clinically, tightness of this sphincter can result in three types of symptoms. The most benign symptom is isolated chronic pain, felt below the rib

cage on the right side. The diagnosis is made by measurement of the pressure inside the sphincter. A pressure equal or exceeding 40 mm of mercury is consistent with increased pressure and contraction of sphincter of Oddi (SD). More serious clinical conditions arise from damage to the liver and pancreas due to back up of bile flow or pancreatic enzymes into these vital organs. In these cases, patients may develop severe fatigue, poor digestion and /or jaundice (yellow skin) due to the liver failure, in addition to local abdominal pain and discomfort.

Treatment of SO contraction is difficult. Oral medications are not helpful. Surgery (cutting the muscle fibers of the SO) is also often not helpful and is associated with serious risks such as bleeding, perforation or inflammation of the pancreas. Several pilot studies (not placebo controlled) have shown that injection of Botox into the SO relaxes this muscle and reduces the inside pressure of SO substantially. Pain relief occurs in 50% of the patients following Botox injection; also, some patients do better after surgery if they have Botox injection prior to surgery. Longterm follow ups are needed to determine the role of Botox injections in relieving the symptoms of SO dysfunction.

The effects of Botox injection into SO for patients who have had partial removal of their pancreas due to tumor or inflammation have been explored recently. (tumor, infection). Many of such patients develop a fistula in the pancreas after surgery that complicates their recovery. In one study, injection of Botox into SD significantly decreased development of fistula in the pancreas after partial resection and improved the patient outcome.

Hypertensive Esophageal Disorders

This group of esophageal motility disorders includes diffuse esophageal spasm and nutcracker esophagus. The problem seems to be related to hyperexcitability of the esophageal muscle itself related to decreased activity of inhibitory nerve cells in the brain or enhanced effects of previously described nerve-muscle transmitter acetylcholine. Affected patients complain of difficulty in swallowing (dysphagia), nausea, chest pain and regurgitation.

Medical treatment includes drugs that are commonly used for treating depression such as tricyclic agents and calcium channel blocking agents. Oral nitrate, sildenafil (50 mg) and isosorbide (10 mg) are the next line of treatment. If these measures fail, Botox injections are recommended. Usually, 100 units of Botox is diluted in 4 ml of saline and injected into multiple sites in the lower esophagus, extending from the region of LES to 5 cm and sometimes even farther upward. Between 70–90% of patients respond well to Botox injections with improvements apparent within 30 days. The injections are particularly effective in improving swallowing but have little effect on other symptoms. A repeat injection is required in 6–24 months to maintain the acceptable level of efficacy.

Partial Paralysis of the Stomach -Gastroparesis

Both sympathetic and parasympathetic nervous systems provide innervation to the stomach. Normal function of these nerves which activate and relax smooth muscles of the stomach controls gastric emptying. Gastroparesis is defined by delayed gastric emptying in the absence of a mechanical obstruction. Gastroparesis is much more common in women than men with a prevalence of 38 and 9.6/100,000, respectively [5].

The symptoms of gastroparesis include nausea, vomiting, bloating, excessive fullness after eating, weight loss, abdominal pain and early satiety. Patients may ignore the mild early symptoms for a longtime before seeking medical care. The diagnosis of gastroparesis is made most efficiently by a 4-hour gastric emptying scan.

In approximately, half of the patients with gastroparesis, despite modern medical work up, the cause remains elusive. Common diseases associated with delayed gastric emptying are diabetes, Parkinson's disease, multiple sclerosis, surgical or accidental injury to the vagus nerve (a part of the parasympathetic nervous system) that contracts the stomach muscles and controls the function of pyloric sphincter- circular muscle that controls opening of the stomach into the gut. Movements of the stomach and control of the pylorus are not under conscious control. Excess of certain medications also can cause delayed stomach emptying; most notable among these medications are high doses of narcotics and certain drugs that are used for treatment of Parkinsons disease (Dopamine agonists).

Treatment of delayed gastric emptying starts with dietary counseling and nutritional management. In advanced cases, feeding may have to be done via a tube that delivers food directly to the first part of the gut through a hole opened in the abdomen. The most effective medication for improvement of gastroparesis is a drug called metoclopramide (Reglan) that reduces the effect of dopamine. Surgical treatment focuses on cutting the muscle fibers of the pylorus, electrical stimulation of the stomach or even, in severe cases, removal of the stomach. Many patients remain unsatisfied with the results of these medical and surgical treatments.

The first data on the use of Botox injections in gastroparesis was published in 2002 [6]. Injection of 100 units of Botox into the pylorus (the sphincter between the stomach and the first part of the gut) in patients with gastroparesis secondary to diabetes has improved the symptoms of 50% of the patients as well as showing improvement of the gastric emptying tests. In some studies, the dose was increased to 200 units. Younger patients, women and those patients with unknown cause of their gastroparesis responded better to Botox therapy. The response usually lasts 4–5 months.

Unfortunately, a couple of high quality studies that compared the results of Botox injections with placebo, despite showing improvement of gastric emptying tests, failed to show substantial improvement in patients' symptoms. Furthermore, some reports claim that stomach lining may change and harden after Botox injections, the long-term effects of which are not clear. Due to these issues and concerns,

currently, Botox injection into pylorus remains a debatable approach for treatment of gastroparesis. Some specialists practice it, whereas others refrain from use of Botox for management of gastroparesis.

Anismus – Painful Contraction of the Anal Sphincter and Nearby Muscles

In this condition, external anal sphincter and the muscle attached to it (puborectalis muscle) that connects pubis to rectum, develop high tone and interfere with defecation. In many cases of anismus, instead of relaxing at the initiation of defecation, anal sphincter and puborectalis muscle (PR) contract and make defecation painful and uncomfortable. Anismus can result from surgery of the ano-rectal area, hysterectomy, trauma to the region and even stress but, in many cases, the cause remains undetermined.

Treatment of anismus is difficult. Soft dietary regimen and improving stress is helpful in some patients. Special biofeedback sessions have been reported to help but, success is limited. In severe cases, surgery is recommended. Cutting some fibers of the sphincter and PR muscles reduces the tightness of these muscles and can provide relief in over 50% of the patients. Surgery, however, carries the risk of fecal incontinence and infection.

Application of botulinum toxin therapy for treatment of anismus was first reported by Dr. Hallan and his associates in 1988; they reported significant improvement of constipation in seven patients [7]. In a review of the subject in 2016, Hany Emile and coworkers revealed 11 publications on this subject [8]. The average rate of success was 77% after the first injection. Approximately 45% of the patients were still satisfied 4 months after treatment. The incidence of side effects was 7% and included two patients with fecal incontinence (mild and transient) and one with rectal prolapse. The side effects with Botox injections are, in general, lower than that of surgery, but treatment needs to be repeated in over half of the patients every 4–6 months. Both Botox and Dysport (another type A botulinum toxins) were found to be effective in treatment of anismus. Injections are performed using a thin 27.5 or 30 gauge needle following application of local anaesthesia. The use of electromyography (which shows the electrical activity of the muscle) or ultrasound which visualizes the muscle, add to the procedure's accuracy. For Botox, most clinics use a total of 100 units, often divided between anal sphincter and the PR muscle. Injections are done at multiple sites into the muscle.

Anal Fissure

Anal fissure is a tear in the skin of the anal area usually related to increase pressure of the anal sphincter. The torn area leaves a small ulceration and causes significant pain and discomfort during bowel movement**.** Anal fissures can develop acutely or

gradually. Once developed, the healing is difficult due to spasms of the anal sphincter which pulls apart the edges of the fissure exposing the area to inflammation/infection. Passage of hard stool, chronic diarrhea, prolonged vaginal delivery and anal sex are among common causes of anal fissure. Local pain, local bleeding, skin irritation and persistent itch are common complains of the affected patients.

First line of treatment is loosening the stool by using diets high in fiber and drinking lots of water. Taking Sitz baths several times daily helps local discomfort. Application of local analgesic creams such as lidocaine jelly (2%) and local creams that make blood vessels relax (vasodilators); nifedipine and nitroglycerin are helpful in management of anal fissure. Persistent and unresponsive anal fissures will require surgery which includes cutting the fibers of anal sphincter in order to make it relax. The procedure is helpful but has a high incidence of fecal incontinence specially in elderly patients and women with multiple childbirths.

Botox injection into the anal sphincter, aiming to relax this sphincter and for management of anal fissure was first described by Drs Jost and Schimrigk in 1993 [9]. Injection of a small amount of Botox (2.5 units) into the external anal sphincter improved the patient's symptoms and helped healing of the anal fissure. Subsequent studies recommended higher doses of 10–20 units. A high quality study (comparing the effect of Botox with placebo) have shown that patients who received Botox injections demonstrated 5 or more times symptom improvement and healing of the anal fissure compared to placebo [10]. Another study of 100 patients with anal fissure demonstrated that patients who received Botox injections into the anal sphincter had significantly less incidence of fecal incontinence compared to surgical sphincterectomy; 7% verssus 33%) [11]. Botox injections need to be repeated every 4–6 months. Botox therapy for management of anal fissure is, therefore, effective and remains a good alternative for patients who do not want surgery or those who are at high risk for development of fecal incontinence after sphincter surgery.

Alimentary Problems Related to Tongue Dyskinesia (Involuntary Movements).

Involuntary movements of the tongue are seen most commonly following exposure to certain medications which interfere with the action of an organic chemical called dopamine. Dopamine is present in abundance in brain cells and contributes to the function of motor system. Drugs that block the action of dopamine are now widely used in psychiatry for treatment of schizophrenia and mood disorders. Unfortunately, chronic exposure to these drugs may damage brain cells and causes involuntary movements (tardive dyskinesia). Sometimes these movements are short-lived; sometimes they can persist for a long time, even for life. Involuntary movements of the tongue are often associated with involuntary movements of the face and lips. Tongue movements are often multidirectional, side to side, rolling and sometimes protruding. Involuntary tongue movements are also seen sometimes in certain neurological disorders that involve the brain.

Treatment of tongue movements in tardive dyskinesis(often related to chronic use of neuroleptic drugs) is very difficult. In lucky patients, the movements are self-limiting and disappear within days or months after onset. For those with persistent tongue movements, a drug called tetrabenazine which works on the dopamine system offers partial help.

Injection of botulinum toxins into the tongue can slow down the tongue movements and improve patients' alimentation as well as speech. Recent studies have shown that injection of the tongue in tardive dyskinesia by diminishing the tongue movement can significantly improve the patients' quality of life [12]. The treatment, however, is risky and over dosing can lead to tongue paralysis for 2–5 months causing significant feeding problems. In experienced hands, however, most patients are happy since reduction of involuntary tongue movements improves alimentation and quality of life. I use a ½ inch or ¾ inch long needle (gauge 27.5 mm) through a lateral approach. If using Botox, a starting dose of 5 units/side is usually effective and pleases the patient (although the tongue movements may not totally cease). The dose may be increased to 7.5 units per each side of the tongue in subsequent injections. The effect of Botox usually lasts 3–4 months.

Conclusion

Hyperactivity of sphincter muscles can cause problems with passage of food through different parts of the alimentary system. Botulinum toxin injections by reducing sphincter's muscle tone can help proper passage of food and improve patient's alimentation. Botulinum toxin therapy is effective in management of anal fissure. In medical disorders that result in involuntary tongue movements, injection of botulinum toxin into the tongue can reduce movements and improve the patients' quality of life.

References

1. Safarpour Y, Jabbari B. Botulinum toxin treatment of movement disorders. Curr Treat Options Neurol. 2018;20(2):4. https://doi.org/10.1007/s11940-018-0488-3.
2. Schneider I, Thumfart WF, Pototschnig C, Eckel HE. Treatment of dysfunction of the cricopharyngeal muscle with botulinum A toxin: introduction of a new, noninvasive method. Ann Otol Rhinol Laryngol. 1994;103(1):31–5.
3. Sharzehi K, Schey R. The role of botulinum toxin in gastrointestinal tract. In: Jabbari B, editor. Botulinum toxin treatment in clinical medicine. Cham: Springer; 2018. p. 67–80.
4. Alfonsi E, Restivo DA, Cosentino G, et al. Botulinum toxin is effective in the management of neurogenic dysphagia. Clinical-electrophysiological findings and tips on safety in different neurological disorders. Front Pharmacol. 2017;8:80. https://doi.org/10.3389/fphar.2017.00080. eCollection 2017

5. Jung HK, Choung RS, Locke GR, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. Gastroenterology. 2009;136(4):1225–33.
6. Ezzeddine D, Jit R, Katz N, Gopalswamy N, Bhutani MS. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. Gastrointest Endosc. 2002;55(7):920–3.
7. Hallan RI, Williams NS, Melling J, et al. Treatment of anismus in intractable constipation with botulinum a toxin. Lancet. 1988;2(8613):714–7.
8. Emile SH, Elfeki HA, Elbanna HG. Efficacy and safety of botulinum toxin in treatment of anismus: a systematic review. World J Gastrointest Pharmacol Ther. 2016;7(3):453–62. https://doi.org/10.4292/wjgpt.v7.i3.453.
9. Jost WH, Schimrigk K. Use of botulinum toxin in anal fissure. Dis Colon Rectum. 1993;36(10):974.
10. Maria G, Cassetta E, Gui D, et al. A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. N Engl J Med. 1998;338(4):217–20.
11. Jost WH. One hundred cases of anal fissure treated with botulin toxin: early and long-term results. Dis Colon Rectum. 1997;40(9):1029–32.
12. Nastasi L, Mostile G, Nicoletti A, et al. Effect of botulinum toxin treatment on quality of life in patients with isolated lingual dystonia and oromandibular dystonia affecting the tongue. J Neurol. 2016;263:1702–8.

Chapter 10
Botulinum Toxin Therapy in Joint and Bone Problems – Emerging Literature Radiates Hope

Introduction

Botulinum neurotoxin (BoNT) is produced by a bacteria present in nature. It causes serious illness when it enters the human body in large amount through contaminated food. When used in medicine, the toxin is quantified in units, each unit reflecting certain degree and percentage of mortality among exposed mice. The contaminated food that causes illness in human usually contains hundreds of thousands or even millions of toxin units, whereas the amount used for medical treatment (through injection) is in most cases below 400 units.

The molecular structure of the botulinum toxin, history of its development as a therapeutic agent in medicine, and the different kinds of botulinum toxin are described in detail in the first three chapters of this book. In brief, of the 7 subtypes of the toxin, only types A and B are currently used in medicine due to their long duration of action. Three variants of the type A toxin are FDA approved under the trade names of Botox, Xeomin and Dysport, whereas only one type B toxin-Myobloc- is FDA approved. The toxin units are not exactly comparable, in clinical research, the following approximations are used:

Each 1unit of Botox = 1 Unit of Xeomin = 2.5–3 unit of Dysport = 40–50 units of Myobloc. For medical use, botulinum toxin is only used via injection either into the muscle or into/under the skin. Xeomin vials do not need refrigeration, whereas the other three toxins require refrigeration due to their heat sensitivity. Myobloc is provided as a prepared solution ready for injection, whereas, other the three type A toxins, need to be diluted with saline (salt water) before injection (see Chaps. 2 and 3 for details).

After injection, the carefully prepared and titrated toxin reaches the nerve ending and the region of nerve -muscle junction. It is in this junction that after entering the nerve ending the active moiety of the toxin -light chain (see Chap. 1) prevents release of certain chemicals which are essential for transmission of the nerve signal to the muscle and for muscle activation. In the sensory system botulinum toxin

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_10

molecule blocks the function of sensory transmitters that relay the pain sensation to the brain. It is this effect over the pain transmitters that is of great interest in many medical disorders- inclusive of joint and bone disorders- in which the patients are afflicted by pain.

In his chapter, we will discuss the effect of botulinum toxin treatment on the pain associated with chronic osteoarthritis, tennis elbow, pain after total knee replacement and joint pain caused by imbalance of attached muscles.

Pain of Chronic Arthritis (Osteoarthritis)

The word arthritis describes inflammation of body joints. Each joint consist of two bones and a fluid filled space (synovia) in between the two, cartilages over the bone surfaces (hard and slick tissue), along with a joint capsule (synovial membrane). There are also ligaments, narrow bands of fibrous tissue that connects the bones together (Fig. 10.1). Except for the cartilages, all structures of the joint including the bones are richly supplied by pain sensing sensory nerves. In addition, in chronic conditions, a cascade of events leads to a phenomenon called sensitization in which many structures that have low pain threshold become sensitive to pain and

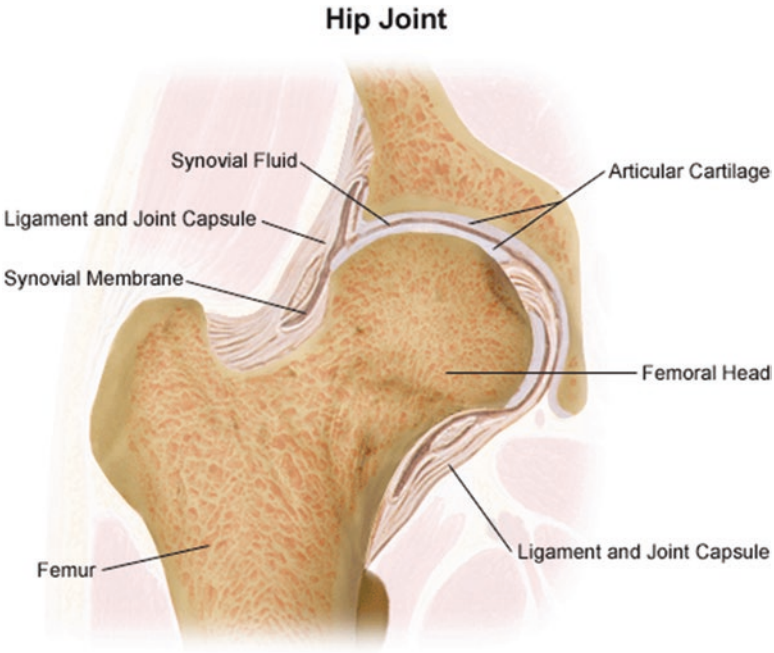

Fig. 10.1 Anatomy of hip joint – A thick synovial fluid is between the head of the long bone of the thigh (femur) and the adjacent pelvic bone, to facilitate movements of the joint. Courtesy of Oxford University Hospitals NHS Foundation Trust- UK

induce pain. Peripheral sensitization is a complicated phenomenon the details of which are beyond the scope of this chapter. In brief, changes in several chemicals known as pain transmitters and modulators enhances the sensitivity of peripheral nerve endings and spinal sensory cells to pain.

Osteoarthritis (inflammation of bone and joint) is the most common cause of pain among all pains involving the musculoskeletal (muscle and bone) system, affecting approximately 250 million people worldwide [1]. During life, 10–12% of all adults, experience osteoarthritic pain [2]. In the US, the number of patients with osteoarthritic pain is growing due to the aging population and effects of obesity. Osteoarthritis is among the leading causes of disability in elderly individuals [1]. The conditions that can be confused with osteoarthritis include trauma to the joint, pain due to ailment of muscles close to the joint and fibromyalgia, a diffuse painful muscle ailment associated with sleep disorder and dysfunction of glands.

Among body joints, the joints that are weight bearing such as hip and knee joints are most often affected by osteoarthritis. Over time and with age, the bones around the joint grow small bone spurs which irritate the nerves and the soft tissues around them. Gradually, local inflammation develops. Inflammation may affect the synovial membrane (Fig. 10.1) and gradually lead to accumulation of fluid in the joint (effusion). The involved joint becomes swollen and painful with pain getting worse during joint activity. In some patients, genetic predisposition attributes to the development of osteoarthritis.

The second most common form of arthritis is rheumatoid arthritis. Rheumatoid arthritis can be seen in many young individuals. Rheumatoid arthritis is a disease of the body's immune system leading to inflammation of the joint capsule with subsequent destruction of cartilage and bone Fig. 10.2.

Symptoms and signs of osteoarthritis include focal joint pain, joint stiffness, redness, joint swelling and limitation of joint movements. These symptoms increase with age and often lead to disability. Tests that are used for imaging the joints are useful in showing the extent of bone and cartilage damage. Among these tests, MRI is most accurate since it provides detail definition of bone and soft tissues.

Conventional treatment of arthritis includes multiple strategies. The results of these treatment strategies are usually modest and, in most patients, the level of pain relief is not satisfactory [1]. Medical treatment is often combined with physical therapy that includes exercises designed to improve the range of motion along with strengthening of the joints. Heat pads and ice packs may help to alleviate pain. In obese individual loss of weight is recommended. Massage of the affected joint, acupuncture and Yoga can also provide various degrees of pain relief.

Mild cases of osteoarthritis are treated by commonly used pain killers such as aspirin or Tylenol. The drugs that specifically target inflammation but are not in the steroid category such as motrin and advil are also frequently used for treatment of osteoarthritis. More severe cases require steroid therapy. Steroids can be taken orally (prednisone) or injected directly into the joint. Injection of hyaluronic acid into the joint has been shown to be helpful in some patients. This material which has a viscosity similar to synovia (joint fluid) coats the bone surfaces and prevents further bone damage.

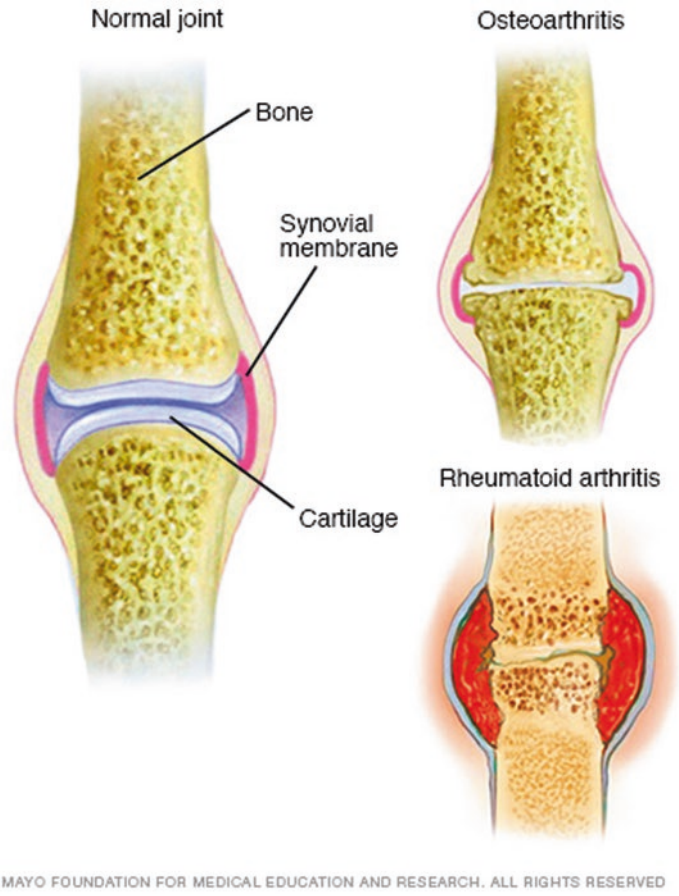

Fig. 10.2 Normal joint and joints affected by osteoarthritis and rheumatoid arthritis. Printed with permission from the Mayo foundation

Surgery includes joint fusion, repair and replacement. Joint fusion is used for smaller joints such as those of fingers and wrists. In the repairing procedure, the surgeon cuts across the bone above and below the joint, removes part of the bone and insert new bone in order to shift the weight away from the damaged part of the joint. For worn out joints, joint surfaces are replaced by metal or plastic parts.

Botulinum Toxin Therapy in Osteoarthritis (OA)

The modest effect of medical therapy in osteoarthritis, and reluctance of many patients with OA to have surgery, encouraged investigators to explore the efficacy of botulinum toxin injections for alleviation of pain in OA. As was discussed earlier,

animal studies have shown that injection of BoNTs into muscle inhibits release of pain transmitters from nerve endings and alleviates pain. Following the observation that Botox injected into dog's joints with arthritis relieves joint pain, researchers began to study its effect on human joints affected by osteoarthritis. Dr. Mahowald and his colleagues first reported that injection of Botox into the shoulder (100 units) or limb joints (25–50 units) can alleviate pain of arthritis in humans [3]. Other investigators subsequently found that injection of other type A toxins as well as B toxin into the human osteoarthritic joints can relieve this type of pain as well.

In a recent, high quality study, authors compared the effects of Botox with placebo (salt water) injection into the shoulder joints of 121 patients with OA. The study was blinded meaning neither the injecting doctor nor the patient knew what was injected (Botox or placebo). Half of the patients received Botox. The effect of injections was assessed by another doctor not involved in preparing the Botox or performing the injections. Standard scales for evaluation of joint pain, patients, quality of life and patients' degree of disability were used to assess the efficacy of the treatment over months of follow up after injections. The researchers found that Botox injection was statistically superior to placebo in regard to pain relief, improvement of quality of life and patient disability [4]. Botox and placebo groups had the same number of side effects which were all minor and self-limiting. The finding of this study are in agreement with the results of a recent review on the safety of BoNT injections in OA which has found no patient in all reported studies of BoNT therapy for OA reported any significant side effects after joint injections [5]. Using the criteria of the American Academy of Neurology (AAN), the level of efficacy of BoNT therapy for relieving pain of osteoarthritis is B (probably effective); this is based on availability of two high quality class II studies. The reader is referred to Chap. 3 of this book for definition of efficacy levels and class of the research studies (I, II, III, IV) based on the published guidelines of the AAN.

Tennis Elbow (Lateral Epicondylitis)

Rungue, in 1873, coined the term "tennis elbow" for a pain disorder which involves the elbow and causes an ailment in tennis players. It is believed that players with a strong back hand repeatedly traumatize the tendon of one of the extensor muscles of the wrist (short extensor) which is attached to the lowest part of the long bone of the arm called lateral epicondyle (Fig. 10.3). As a result of repeated trauma, multiple small tears develop in the tendon (where muscle attaches to the bone) and initiate pain.

Subsequent observations revealed that this form of muscle and bone injury is not limited to tennis players and a wide range of trauma to this region can cause it (weight lifting, certain jobs that require pulling and bending the elbow). Currently, the term lateral epicondylitis (LE) which means inflammation of lateral epicondyle (Fig. 10.3) is used more frequently in place of tennis elbow since the damaged

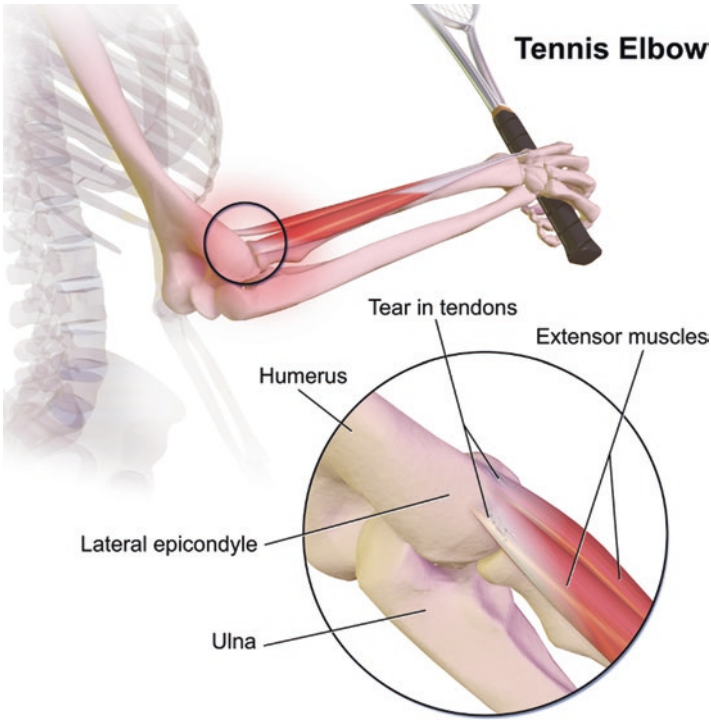

Fig. 10.3 Tennis elbow is caused by tears in the extensor wrist muscles close to lateral epicondyle of the elbow. From Wikemedia commons- licensed under creative commons attribution

muscle close to lateral epicondyle often manifests some degree of inflammation (accumulation of reactive blood cells in the issue).

Lateral epicondylitis involves 1 to 3% of general population over their life time. Men and women are equally affected with the age of onset being between 35–55 years. Most patients gradually recover from this condition over 6–24 months. In 5–10% of the patients, however, the condition continues and becomes the cause of chronic elbow and forearm pain [5]. Affected patients feel the pain in the area of the elbow with radiation to the forearm. In some patients with chronic pain, examination shows some limitation of wrist and finger movements. X-ray examination of the elbow shows local deposits of calcium in 25% of the patients. The MRI usually shows no significant bone or soft tissue pathology. For most patients, surgery is not necessary unless a serious pathology is suspected (tumor, infection, etc)

Several medical and non-medical approaches have been tried for management of pain in chronic LE. These include exercise therapy, taping the elbow, laser therapy, applying braces, acupuncture, and ultrasound therapy. Platelet-rich plasma injections is an expensive approach in which the patients' own blood is centrifuged and the buffer zone on the top (rich in platelets- blood cells which help to stop bleeding) is injected in the area of pain. The results of these strategies in chronic LE are at

best, modest, and consist of temporary pain relief. Furthermore, the lack of high quality studies makes it hard to discern the utility of these approaches. Local patches of glyceryl trinitrate have helped relieve pain in one high quality study (using placebo as control) but the results were temporary. In another high quality study, injection of hyaluronic acid gel into the joint, in a manner similar to that used in OA, reduced the patients' pain[6]. Injection of steroids (triamcinolone) into the joint has been used also for pain relief, but it has a high relapse rate. Different surgical approaches for management of LE associated pain have been used; some have succeeded to relieve the pain for 12 months.

Botulinum Toxin Treatment

Recognition of the pain killer effect of local botulinum toxin injection (now approved by FDA for treatment of migraine), encouraged investigators to study this mode of treatment for pain relief in LE. Over the past 15 years, more high quality studies (blinded, placebo controlled) have been performed using botulinum toxins in LE than any other mode of treatment for management of LE associated pain. Of 7 high quality studies published to date in this area, 4 blindly compare the effect of botulinum toxin with placebo and 3 compare the effect of botulinum toxin with steroids. In the placebo- controlled studies, authors used Dysport, a type A botulinum toxin, similar to Botox (see Chap. 3). Injections were performed either close to the painful epicondyle or a few centimeters lower into the short extensor muscle that is attached to the lateral epicondyle (Fig. 10.3). A total of 50–60 units of Dysport, roughly equivalent to 20–25 units of Botox, was used, and injected into 2 to 3 muscle sites. Among the four studies that compared the effect of Dysport with placebo, three have shown that BoNT therapy is clearly superior to placebo in reducing pain and improving the quality of life. In the comparator studies, both BoNT and steroid injections improved elbow and forearm pain. While the level of pain relief was initially higher in those patients who received steroids, patients who received BoNT injections demonstrated a more sustained pain relief which lasted 3–6 months. This data indicate that injection of botulinum toxin into the extensor muscle of the forearm close to the elbow is a reasonable alternative to surgery for management of intractable pain in chronic LE. A level B evidence level, probably effective (Using AAN's criteria- See Chap. 3), can be given to botulinum toxin therapy for relieving pain of tennis elbow based on the number of positive high quality studies. The drawback of botulinum toxin therapy for tennis elbow is development of weakness of finger extension that is seen in 30–40% of the patients after injection into the short extensor muscle of the forearm. Unfortunately, once developed, finger weakness can last up to 2–4 months. Future studies using smaller doses and more refined methods of botulinum toxin injection may overcome this unpleasant side effect.

Pain After Total Knee Replacement (Arthroplasty)

Advanced osteoarthritis of the knee which is associated with degeneration and destruction of the knee joint limits the patients' activity and may progress to total immobility. Total knee replacement - total knee arthroplasty (TKA)- is a common procedure for retaining the knee function. In 2010, the number of total knee replacements in the US was 719,000 [7]. It is estimated that over half of all patients with chronic knee osteoarthritis will undergo TKA. Modern knee replacement techniques using the latest and most advanced hard-wares have been very successful in improving the range of knee movements and improving patient's ambulation. Surgery is usually done under general anesthesia.; an alternative is spinal anesthesia which numbs the body below the waist. With spinal anesthesia, the patient has the option to remain conscious during the operation.

Unfortunately, 10–34% of the patients develop chronic knee pain after total knee arthroplasty that greatly impairs their quality of life. The pain can be a newly developed pain or an enhancement of the pain that the patient experienced before surgery [8]. A number of factors have been associated with development or exaggeration of knee pain after total knee surgery; these factors include having a high level of pain before surgery, presence of other painful muscle or joint disorders and poor mental condition of the patient [9].

Management of sustained pain after total knee arthroplasty consists of physical therapy, stretch exercises and use of pain killers. Steroid injection into the soft tissue and around the painful knee joint has been reported to relieve pain in some patients. However, all studies are open label (no placebo for comparison) and, hence, the results are colored by a moderate to high degree of bias.

Botulinum Toxin Therapy

Dr. Singh and his colleagues conducted a high quality study on 49 patients among whom, 60 knees had total arthroplasty [10]. Thirty legs received 100 units of Botox, diluted in 5 ccs of saline injected into the knee joint, whereas the other 30 legs received 5 cc of saline (salt water, placebo) only while using the same methodology. The patients' mean age was 67 years. In the Botox group, 22% of the patients were female. Patients' response was evaluated by several outcome measures among them three scales designed specifically to assess pain. A WOMAC scale (western Ontario McMaster Universities osteoarthritis index) was also used to assess functionality, joint stiffness and pain. Patients were followed for 6 months after a single set of injections.

At two months, the WOMAC osteoarthritis scale showed significant improvement of all three of its subsets (pain, functionality and stiffness) in patients who received Botox injections but not in the placebo group. There was also a marked difference between the Botox group and the saline group in regard to response to

pain in the pain specific scales. A notable pain relief was noted in 71% of the patients who had received Botox injections versus 35% in the placebo group. Side effects were minor, consisting of transient local pain after injection and occurred with comparable frequency between the two groups (Botox and placebo). This positive, high quality class II study (see Chap. 3 for class definition) indicates that Botox injection into the knee joint is possibly effective to relieve recalcitrant pain of total knee arthroplasty. Botox injection into the knee joint may be tried when other management strategies fail to relieve this form of pain.

Chronic Knee Pain due to Imbalance of Vastus Muscles

A common cause of chronic knee pain is poor balance between the activity of lateral and medial muscles of the thigh (vastus muscles). Vastus muscles along with rectus muscle extend the knee.

Over activity of the lateral vastus muscle (vastus lateralis) or/and delayed activity of medial vastus muscle leads to misalignment of the patella (knee's funny bone) and causes chronic pain in front of the knee (Fig. 10.4). The patella gradually shifts laterally and tilts. The pain is felt in the front of the patella and is provoked by ascending or descending stairs, kneeling, squatting and prolonged sitting [11]. It is a debilitating condition which is more common among young women. This condition is also called

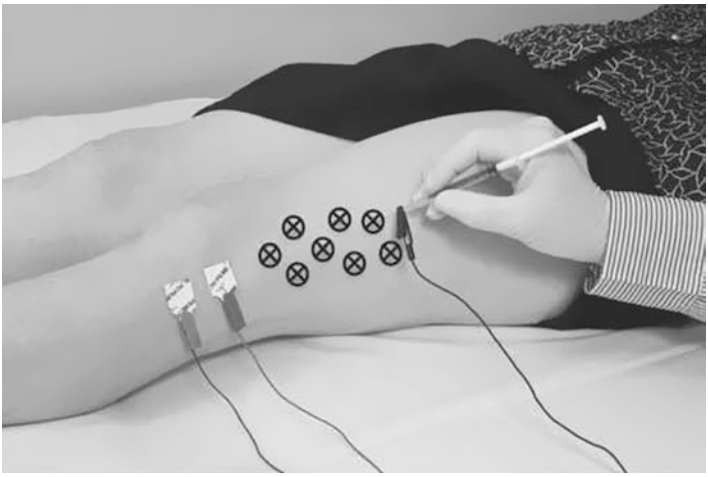

Fig. 10.4 Method of botulinum toxin injection used by Singer and co-workers for treatment of vastus lateralis imbalance. Reproduced with permission from the BMJ Publishing group. The injecting syringe is connected to an EMG needle that identifies the muscle via the sound of its electrical activity. A total dose of 500 units of Dysport is injected into eight sites (designated by Xs) into the vastus lateralis muscle

patello-femoral syndrome (PFS). In 2008, the number of patients affected by the PFS was estimated as 971,000 costing the U.S. economy $8.3 billion (www.pearldiverinc.com).

Imaging of the knee joint (X-ray/MRI) usually do not show any abnormality. The goal of treatment is to reduce pain and swelling, improve the balance between vastus medialis and vastus lateralis muscles, restore normal gait, and improve postural control of the lower extremity. Short -term taping of the patella associated with special exercises to strengthen the thigh muscles provides partial pain relief. Many patients use common pain killers with degrees of success. Surgery is hardly indicated. High quality studies are not available to compare different methods of treatment in PF syndrome.

Botulinum Toxin Treatment of VLS

In 2010, Dr. Singer and his colleagues reported on the results of a study that compared injection of Dysport (a botulinum toxin type A) with placebo (salt water) in 24 patients with vastus lateralis(VL) imbalance (PFS) [12]. In the toxin group, 500 units of Dysport (roughly equal to 200 units of Botox) was injected at 8 points into the VL muscle (Fig. 10.4). The same injection methodology was used for the saline group. The pain and functionality was evaluated through standard scales, blindly, at 3 months. Patients who received Dysport injections showed significant improvement in walking, stair climbing and squatting, whereas those who received placebo did not. Furthermore, there was a marked reduction of knee pain on the visual analogue scale, a 0–10 level of pain reported by the patient. There was no significant side effects after Dysport injections. This high quality study, rated class II, suggests that botulinum toxin injection into vastus lateralis muscle is helpful in relieving pain and improving functionality of patients with PFS. The dose of Dysport used in this study was safe and did not produce significant muscle weakness or any other unwanted side effects.

Conclusion

Botulinum toxin injection into the joint effectively improves pain of chronic osteoarthritis as well as chronic knee pain after total knee replacement surgery (arthroplasty). Injection of Botulinum toxin into the lateral muscle of the thigh (vastus lateralis) corrects the imbalance between lateral and medial thigh muscles via decreasing the tone of this muscle and consequently relieves the chronic knee pain at the region of the patella (front of the knee). High quality studies have shown that botulinum toxins therapy for these indications (with applied doses) is safe and well tolerated by the patients.

References

1. Neogi T. Structural correlates of pain in osteoarthritis. Clin Exp Rheumatol. 2017, September–October; 35 Suppl 107(5):75–78. Epub 2017 Sep 29.
2. Dunlop DD, Manheim LM, Song J, Chang RW. Arthritis prevalence and activity limitations in older adults. Arthritis Rheum. 2001;44:212–21.
3. Malhowald ML, Singh JA, Dykstra D. Long term effects of intra-articular injection of botulinum toxin A for refractory joint pain. Neurotox Res. 2006;9(2–3):179–88.
4. Arendt-Nielsen L, Jiang GL, DeGryse R, et al. Intra-articular Onabotulinum toxin A in osteoarthritis knee pain: effect on human mechanistic pain biomarkers and clinical pain. Scand J Rheumatol. 2017;46:303–16.
5. Nguyen C, Rannou F. The safety of intra-articular injections for the treatment of knee osteoarthritis: a critical narrative review. Expert Opin Drug Saf. 2017;16(8):897–902.
6. Luk JKH, Tsang RCC, Leung HB. Lateral Epicondylalgia: midlife crisis of a tendon. Honk Kong Med J. 2014;20:145–51.
7. Centers for Disease Control and Prevention. Number of all-listed procedures for discharges from short-stay hospitals, by procedure category and age: United States, 2010. Atlanta: Centers for Disease Control and Prevention; 2010.
8. Beswick AD, Wylde V, Gooberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012;2:e000435.
9. Beswick AD, Wylde V, Gooberman-Hill R. Interventions for the prediction and management of chronic postsurgical pain after total knee replacement: systematic review of randomised controlled trials. BMJ Open. 2015 May 12;5(5):e007387. https://doi.org/10.1136/bmjopen-2014-007387.
10. Singh JA, Mahowald ML, Noorbaloochi S. Intraarticular botulinum toxin A for refractory painful total knee arthroplasty: a randomized controlled trial. J Rheumatol. 2010;37(11):2377–86.
11. Pal S, Besier TF, Draper CE, Fredericson M. Patellar tilt correlates with vastus lateralis: vastus medialis activation ratio in maltracking patellofemoral pain patients. J Orthop Res. 2012;30(6):927–33. https://doi.org/10.1002/jor.22008. Epub 2011 Nov 15
12. Singer BJ, Silbert PL, Song S, et al. Treatment of refractory anterior knee pain using botulinum toxin type A (Dysport) injection to the distal vastus lateralis muscle: a randomised placebo controlled crossover trial. J Sports Med. 2011;45(8):640–5.

Chapter 11
Botulinum Toxin Therapy for Involuntary Movements; Dystonias, Tremor and Tics

Introduction

Abnormal involuntary movements are seen during the course of a large number of neurological disorders. Dystonia and tremor are two of the most common forms of these movements. Dystonia and tremor, when severe and disabling, limit the function of limbs and impair the quality of life. Current treatments of dystonia and tremor are partially effective but, often fall short of patients' satisfaction.

Dystonia

Dystonia is defined as a movement disorder characterized by twisting and turning movements inducing abnormal posture in the face, neck and body affected part(s). It is probably the most common form of movement disorder and is seen in a variety of disease conditions. A large number of dystonic problems are genetic and start in early childhood (primary dystonia). These, genetically determined dystonias start focally – usually in one foot, but gradually spread to other parts of the body and, at one point, become generalized. With the passage of time, dystonia gets worse and results in limb(s) fixed in abnormal posture. Patients affected by genetically determined dystonias may have additional symptoms such as weakness of the limbs, walking problems and/or mental deficits.

Focal dystonias with no or low genetic patterns, affect one part of the body and usually remain confined to that part. Most focal dystonias start later in life, usually after age 40. Focal dystonia can affect the face, neck, upper or lower limb. Currently, botulinum toxins are among the first line of management for focal dystonias. Blepharospasm, a focal dystonia of the eyelid muscles was one of the two movement disorders for which FDA approved botulinum toxin therapy in 1989 (see Chap. 1 on history of botulinum toxin therapy).

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_11

Focal Dystonias

A– Focal Dystonias of the Face Region

The two most frequent dystonias of the face which respond to botulinum toxin therapy are blepharospasm and mouth-jaw (oromandibular) dystonias.

1-Blepharospasm

Blepharospasm is uncontrolled, tonic contraction of the muscles (orbicularis oculi/OO) that close the eyelids (Fig. 11.1a) [1]. Spasm of these thin muscles, which are barely under the skin, forces the eyes to close.

Blepharospasm is almost always bilateral and affects both eyes. The eye lid spasms are frequent and can occur hundreds of times per day. Many patients are unable to drive a motor vehicle due to impaired vision. In over 90% of patients with blepharospasm, a cause can not be found (essential blepharospasm). Genetic predisposition is believed to play a role in many of such patients. In rare cases, blepharospasm can be caused by stroke or a brain tumor. Belpharospasm is an uncommon

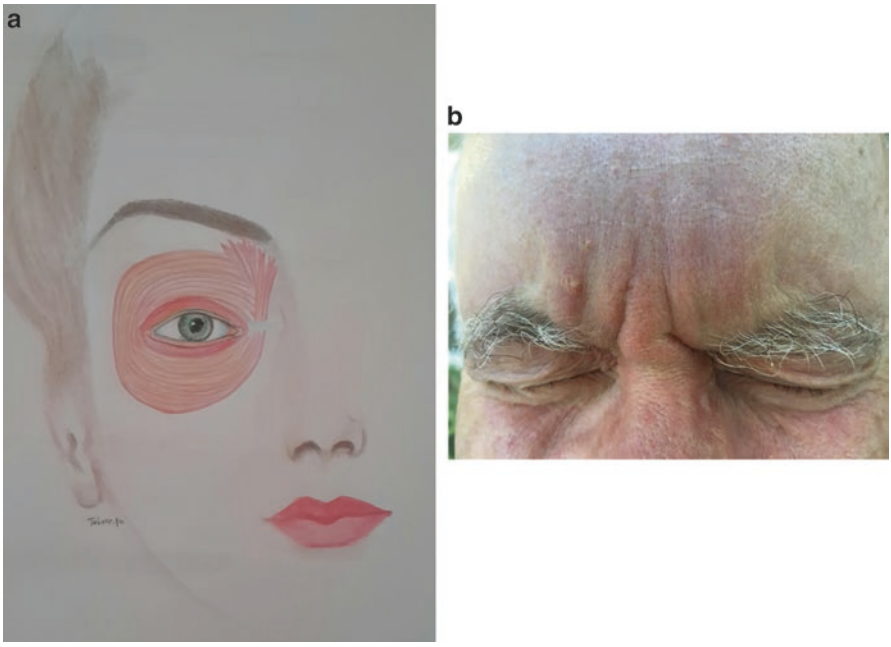

Fig. 11.1 (**a**) Orbilularis oculi muscle. The muscle has a palpebral part that is attached to the lid and an orbital part that is further out and circles the eye. (**b**) belpharospasm closing the eyes

disorder. Approximately 2000 new cases of blepharospasm are diagnosed each year in the United States. Women are affected more often than men with a ratio of 2.8/1 [2]. The onset of blepharospasm is usually after age 40. Blepharospasm should be differentiated from facial tics involving the eye- lids, psychogenic eye closures, and a condition called apraxia of eye- lid opening. The latter, most often seen in elderly with dementias and Parkinson's disease, is due to failure of cerebral cotox to exert proper activation of eye muscles.

Treatment of blepharospasm was disappointing before the introduction of botulinum toxin injections. The commonly used drugs for treatment of blepharspasm are from a group of drugs called anticholinergics. Artane, the most widely used of these drugs in blepharospasm, is provided in 2 mg and 5 mg tablets. Treatment of blepharospasm with Artane requires slow dose escalation starting with 1 mg/day and gradually working up to the effective dose. Most patients respond when the dosage reaches 10-20 mg/day but some patients' require higher doses. Side effects that include blurred vision, severe dryness of the mouth and confusion/hallucinations are especially troublesome in elderly.

Botulinum Toxin Therapy in Blepharospasm

Introduction of botulinum toxins revolutionalized the management of blepharospasm. The toxin is prepared by diluting the powdered preparation (provided in a small vial) in an small amount of salt water (saline), and injected with a very thin needle around each eye. Injections are performed close to the eye and introduced barely under the skin into the orbicularis oculi (OO) muscle. Usually 5 to 6 locations around each eye are injected (Fig. 11.2). Initial sites of injection can be later modified in subsequent injections.

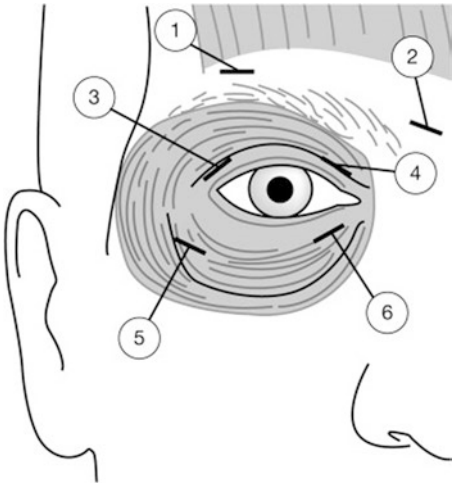

Fig. 11.2 Sites of initial botulinum toxin injection for treatment of blepharospasm advocated in a large multicenter study. Injections are around both eyes. From Troung and co-workers 2012- Reproduced with permission from the publisher- Elsevier [4]

The author of this book uses a similar scheme with a minor change from the above scheme for the initial injection; I use an additional injection between sites 5 & 6, but do not include site #2 in initial injection scheme(unless the area is clearly active).

Over 90% of the patients with blepharospasm respond well to botulinum toxin injections [3]. Patients note the result within 2–3 days, the peak effect becomes apparent within 10–14 days and the effect lasts for 3–4 months. Injections cause mild discomfort; in experienced hands, side effects are uncommon and minor; the patient may experience seconds of pain in the area of injection and minor local bleeding. Drooping of upper eye lid, can now be avoided by either not injecting at midline close to the upper lid (in proximity of the muscle that lifts the upper eyelid) or injecting at midline above the eyebrow (Point # 1 in Fig. 11.1) with small amount of toxin (in case of Botox, not to exceed 2–2.5 units).

We usually start with 2.5 units of Botox in six locations which in many patients suffices to stop the spasms. Later, when the injector becomes more familiar with the patient's facial response to injections, the dose may be increased in one or more of the above- mentioned locations, to 3–5 units/site. Other marketed and FDA approved botulinum toxins (Xeomin, Dysport)) are also effective in management of blepharospasm (see Chap. 3 for description of the four FDA marketed botulinum toxins in the US). In severe cases of blepharospasm, the injections may include an additional injection into the upper cheek muscles and/or into the muscles that bring the eyebrows together. The latter muscle (corrugator) is located above the medial part of each eye brow (site 2, Fig. 11.2). Treatment of blepharospasm with botulinum toxins has now a track record of over 27 years and is associated with a high degree of patient satisfaction. Over time, some adjustment of the dose may be required but the dose escalation is usually minor. The treatment is for life since the condition recurs after 3–4 months.

2– Dystonia of the Mouth and Jaw Muscles

Trembling and twitching of the lips, twisting and protrusion of the tongue, locking of the jaw (jaw closure dystonia) and forced jaw opening (jaw opening dystonia) are a group of involuntary movements that can be caused by certain groups of drugs -neuroleptics- used for treatment of psychosis and severe depression. Although the new generation of neuroleptics have fewer of these side effects, these involuntary movements still occur and challenge the psychiatrists. Since these abnormal movements often occur with a delay, the general term of tardive (late) dyskinesia (abnormal movement) is used to designate the abnormal movements in this setting. Neuroleptic drugs are not the only drugs that cause tardive dyskinesia, but they are the prime drug culprits for this form of dyskinesia/dystonias. Dystonias of the tongue, face, lips and jaws may also develop during the course of degenerative diseases that involve deep brain structures (basal ganglia). Many of these disorders resemble Parkinson's disease, but have other symptoms

in addition to slowness of movements, rigidity and tremor. In some of them, a defective gene has been discovered.

Treatment of involuntary, face and jaw movements caused by brain disease or drugs (tardive dyskinesia) is difficult. Valium, Baclofen, Artane, Gabapentine and Tetrabenezine are partially effective, but the effect is usually modest and not sustained. In the lucky patients, the drug induced movements may go away by themselves after weeks or months; once started, however, the movements continue for years or even persist for life in many patients.

Botulinum Toxin Treatment

Injection of botulinum toxin into the muscles involved by involuntary jaw movements results in at least moderate, sustained satisfaction in 2/3 of the patients [5]. Luckily, muscles of jaw closure or jaw opening are well known and can be easily identified by examination. The masseter muscle, located at the angle of the jaw and the temporalis muscle located at the temple, are the main muscles that close and lock the jaw (Fig. 11.3a). Both muscles can be easily seen under the skin and activated by asking the patients to clinch their teeth. Furthermore, in patients with jaw closure dystonia, these muscles are increased in size due to their frequent and prolonged contractions. An initial dose of 30 and 40 units (in case of Botox or Xeomin) per muscle/per side may be injected into 2–4 sites into temporalis and masseter muscles, respectively (Fig. 11.3b). In severe cases, the dose may be increased to 50 and 80 units into temporalis and masseter muscle, respectively for subsequent injections if necessary. The effect of Botox lasts 3–4 months.

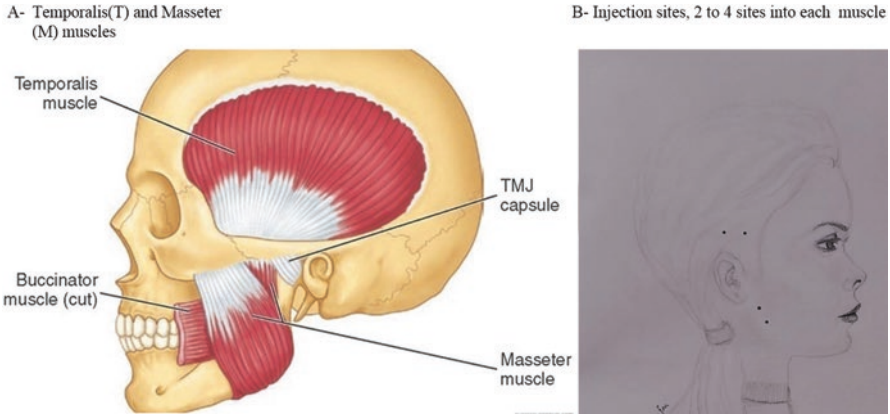

Fig. 11.3 The site of botulinum injection for Jaw Closure Dystonia (JCD). drawing Courtesy of Dr. Tahereh Mousavi **A**- Temporalis(T) and Masseter (M) **B**- Injection sites, 2 to 4 sites into each muscle. Reproduced with permission from Mayo Foundation

Jaw opening dystonia (JOD) also responds well to botulinum toxin therapy, although fewer patients do as well as JCD. This may be due to the fact that muscles for jaw opening are located deeper and harder to reach.

In tongue dystonia, involuntary turning and rolling tongue movements can interfere with speaking and eating. In the author's experience, approximately half of the patients with tongue dystonia respond to injection of Botox into the tongue. Tongue injections require significant expertise and need to be performed by physicians with substantial knowledge in management of difficult dystonias. Overdosing the tongue can cause tongue paralysis and worsen patient's eating and speaking problems. The author starts with a small dose of 5 units (Botox or Xeomin) injected into each side of the tongue; doses higher than 7.5 units per side are not recommended.

Hemifacial Spasm (HFS)

Hemifacial spasm is characterized by involuntary movements involving half of the face. Although hemifacial spasm is not a dystonia (movements are much faster and jerkier), it is mentioned here due to its exquisite sensitivity and remarkable response to botulinum toxin therapy. The movements of HFS are observed around the eye, as well as in the lower face muscles. The movements around the eye involve the OO muscle (see blepharospasm) and, when severe, tend to close the eye. The lower face movements present with twitches in the lower part of the cheek, chin and lips. Hemifacial spasm is not as disabling as blepharospasm but can become the source of serious social embarrassment.

Hemifacial spasm is more common than blepharospasm, affecting 14.5 and 7.4 of women and men in a 100,000 population, respectively [5]. Unlike blepharospasm in which 80% of the cases are essential and have no known cause, in 80% of the patients with hemifacial spasm, the cause is known and is related to an abnormal blood vessel that presses against the facial nerve as it emerges from the lower part of the brain. Chronic pressure against the nerve (for years), leads to the hyperexcitability of the nerve which consequently makes the facial muscles twitch. The condition is not dangerous since the culprit blood vessel almost never ruptures. In a small number of patients, less than 5%, hemifacial spasm can be the result of a brain tumor in the lower part of the brain. It is for this reason that in new cases of hemifacial spasm screening by MRI is indicated.

Oral medications such as benzodiazepines (clonopin and valium), baclofen and gabapentin have minimal effect on hemifacial spasm. Before the introduction of botulinum toxins, many patients required brain surgery during which the surgeon separated the culprit vessel from the facial nerve-releasing the pressure on the nerve. However, HFS surgery could leave the patient with major deficits such as paralysis of the face, loss of hearing and poor balance while walking. Currently, surgery is rarely performed.

In 1989, FDA approved the use of Botox for treatment of hemifacial spasm in the US despite lack of high quality studies (one of the first two approved movement

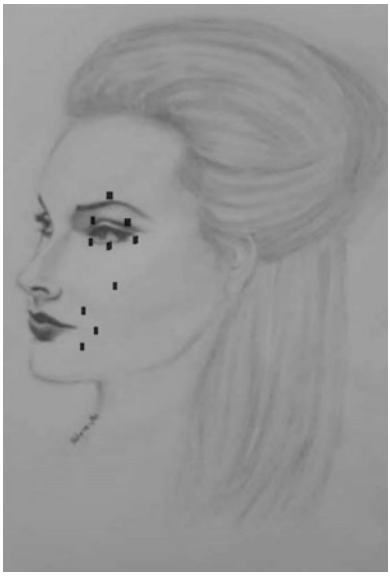

Fig. 11.4 Author's preferred scheme of initial injections for hemifacial spasm. The dose around the eye is 2.5 units/site and in the lower face is 1.5 units/site (for Botox and Xeomin). Drawing, courtesy of Dr. Tahere Mousavi

disorders for which Botox was approved; the other condition was blepharospasm). The published data shows that between 76–100% of the patients demonstrate over 75% improvement with reduction of facial movements after botulinum toxin therapy. Injections are carried by a small, short needle (guage 30. ½ inch) around the eye in a manner similar that used for blepharospasm and also into the lower face muscles starting with a small dose of 1.25 to 2.5 units (in case of Botox or Xeomin) per site (Fig. 11.4). The dose can be adjusted every 3–4 months when reinjection is required. The main side effect of botulinum toxin injection for HFS is weakness of facial muscles that could last for weeks. The lower face muscles are particularly sensitive to botulinum toxin, hence, the initial dose used for lower face should be small (1 to 1.25 unit/site). The issue of facial weakness needs to be discussed with the patient prior to injections for HFS. In practice, many patients prefer not to have lower face injections, at least, not during the first session. Longterm experience with botulinum toxin injections for HFS indicates continued efficacy and low incidence of side effects. Some dose adjustments may be necessary over time. Injections require repeat every 3–4 months. There are now patients with HFS on record, who have been receiving botulinum toxin injections, every 3 to 4 months for 20 years. Since the rate of response is very high (< 90%), unresponsiveness to botulinum toxin therapy should raise the possibility of other disorders such as facial tics or psychogenic facial movements. Experience of the past 20 years has confirm that injection of all types of A toxins (Botox, Xeomin,Dysport) into the appropriate facial muscles effectively reduces the involuntary facial movements in HFS and results in patient satisfaction.

Cervical Dystonia– Dystonia of Neck Muscles

This is another form of focal dystonia that responds very well to botulinum toxin therapy. In this condition, affected patients gradually develop increased tone and contraction of certain neck muscles leading to forced rotation of the neck to one side (torticollis) or neck tilt toward the shoulder (laterocollis). A less common form of CD is when the neck is pulled back (retrocollis) or bent forward (anterocollis) (Fig. 11.5).

The mean age for onset of symptoms in CD is 49 years and there is a strong female predominance (74%) [6]. Over 60% of the patients with CD suffer from chronic neck pain which is more bothersome to some patients than rotation and tilting of the neck. If untreated, the pain gradually intensifies and the intermittent; abnormal neck posture becomes fixed making the neck rigid and immobile. Chronic cervical dystonia is often associated with poor quality of life and a significant degree of disability.

Before introduction of botulinum toxin therapy, CD was treated mainly with a group of drugs that block the function of a chemical called acetylcholine (anticholinergics). Acetylcholine is released at the nerve ending at the point where nerve contacts with the muscle. Anticholinergics are hard to tolerate by older people due

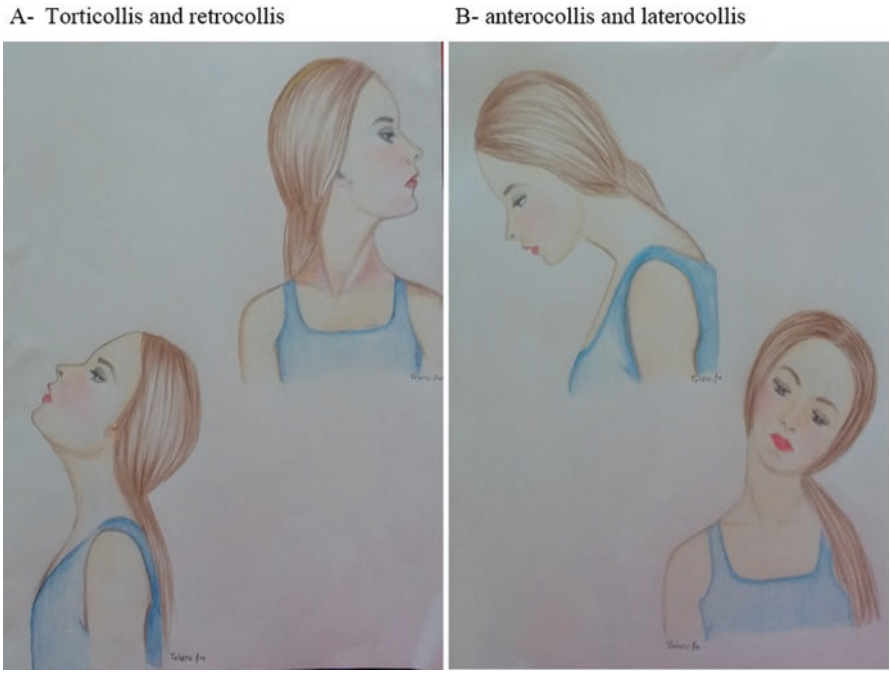

Fig. 11.5 Of the four types of cervical dystonia illustrated above, torticollis (neck rotation) is the most common accounting for nearly half of the patients. Drawing, courtesy of Dr. Tahere Mousavi (**a**) Torticollis and retrocollis (**b**) anterocollis and laterocollis

to dryness of the mouth, blurred vision and confusion that develop as side effects. Other drugs such as baclofen, clonopin and valium are also used alone or in combination.

The efficacy of Botox in treatment of cervical dystonia was first suggested by Dr. Tsui and his colleagues from Canada in a small pilot study in 1985. Based on the results of a large number of published high quality (placebo controlled) published studies over the past 25 years, FDA approved all four of US - marketed botulinum toxins (Botox, Xeomin, Dysport, Myobloc) for treatment of cervical dystonia. Currently, BoNT therapy has become the treatment of choice for management of CD due to its fewer side effects compared to oral medications. In addition, it may either eliminate the need for taking daily oral medications or allows significant reduction of their daily dose. Several studies have shown that improvement of neck posture is associated with marked improvement of associated neck pain [7]. The effectiveness of botulinum toxin therapy in CD is sustained after repeated injections. There are patients on record who have been receiving botulinum toxin injections for cervical dystonia, every 3–6 months for over 25 years. Careful assessments of quality of life have shown that patients' quality of life show notable improvement along with improvements of head and neck posture and neck pain.

A good knowledge of location and function of neck muscles is required in order to succeed with botulinum toxin therapy in cervical dystonia. Some physicians use merely their knowledge of anatomy (anatomic landmarks) for injecting BoNTs into the neck muscles; others, perform the injections under the guidance of electromyography. Electromyography identifies muscles by their electrical activity via a needle which probes into the muscles. A smaller number of physicians use the ultrasound which directly visualizes the muscle and confirms that the tip of the injecting needle is in the right muscle. Like all other indications of botulinum toxin therapy, it is wise to start with a small dose and gradually increase the dose (if necessary) to an effective dose level. For torticollis (rotation type of CD), one could start by first injecting the main neck rotator muscles. If the neck is rotated to the right side, two sets of neck rotators are overactive, one on the right side located in the back of the neck (splenius- Fig. 11.6) rotating the head to the right (same side) and one in the left side (sternocleidomastoid muscle- SCM) located in front of the neck also rotating the head to the right side (opposite side). In case of Botox or Xeomin (with almost comparable units), the author starts with a total dose of 60 units per each muscle injected in three sites (Fig. 11.6). If there is shoulder elevation, trapezius muscle (T) is injected with the same dose. Doses up to 500 units(of Botox) may be required for some patients with severe cervical dystonia (usually not during the first session).

In many patients, however, the problem is more complex, and obtaining a satisfactory response requires injection of a larger number of muscles. Many muscles in the neck have more than one function (rotation, tilt, etc.), the knowledge of which is crucial for treatment of cervical dystonia.

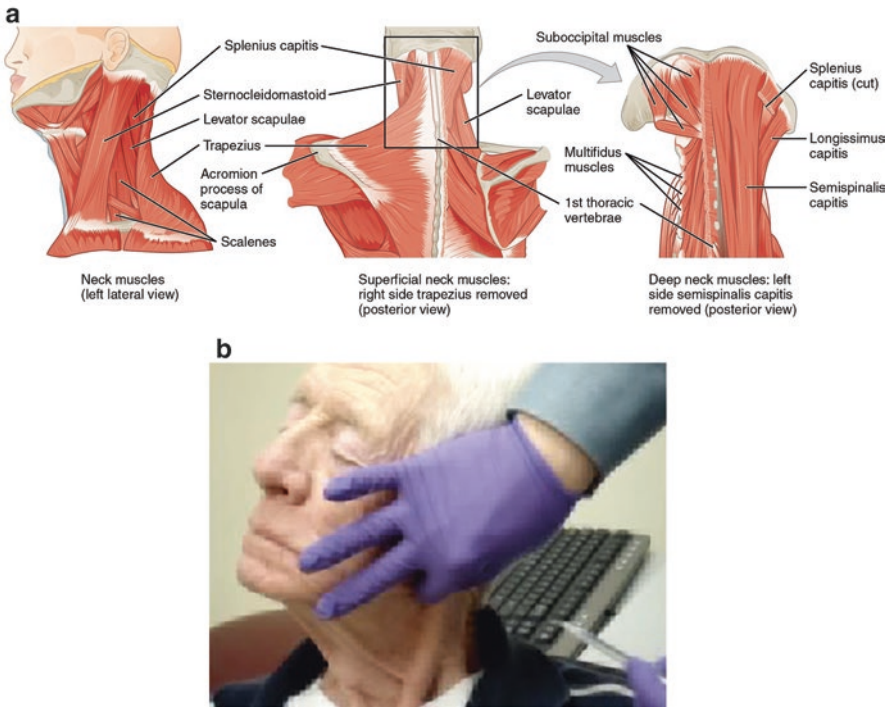

Fig. 11.6 (**a**) Muscle of the anterior and posterior neck, over activity of which can cause different forms of cervical dystonia. From Wikemedia. Reproduced under creative commons attribution (**b**) Injecting an enlarged and hyperactive sternocleidomastoid mmuscle(SCM) forcing the neck to turn right in a patient with severe torticollis

Table 11.I Some commonly injected muscles in cervical dystonia

Muscle pair (right and left	Location	Function
Stenocleidomastoid (SCM)	Front of the neck	Turns the neck to the opposite side, tilts the neck to the same side, bends the neck.
Splenius capitis(SC)	Back of the neck	Rotates and tilts the neck to the same side
Scalenius anterior (SCA)	Front the neck	Tilts the head to the same side
Trapezius (T)	Shoulder	Elevates the shoulder
Elevator Scapulae(LS)	Upper back extending to the front of the neck	Elevates the scapula
		Tilts the head to the same side

Case Report

A 72 year- old man with history of torticollis (rotational cervical dystonia) for 20 years was referred for to the Yale University Botulinum Toxin Clinic for evaluation and treatment. Patient stated that his problem had begun slowly with difficulty in turning his head to the right side. Over months and years, the neck gradually started to turn to the left and for the past 2 years, it had become very stiff and fixed to the left side. Attempting to turn the neck to the right was painful. There was also a head tilt to the left side (most common combination in CD- rotation and tilt). Patient also complained of a fair amount of neck pain which had been bothering him for years. He felt his balance was not good and his quality of life was greatly diminished. Driving was "almost impossible." He was injected with a total of 300 units of Botox into different muscles of the neck (rotators and tilters). One week after Botox injection, there was already demonstrated marked improvement of her neck posture and the ability to rotate his neck to the right side without discomfort. Over the subsequent weeks, he reported notable decrease in his neck pain and believed his quality of life had improved. Over a follow up period of almost 10 years, patient has received repeat Botox injections into his neck muscles every 3 to 4 months. He reported no side effects.

Side effects after botulinum toxin injections for cervical dystonia are usually minor and limited to seconds or minutes of pain at the site of injection and/or transient local bleeding. About 30% of patients may develop some difficulty in swallowing which is usually subtle and is not reported by the patients until asked. Nevertheless, more serious cases of swallowing difficulty may develop after BoNT therapy for CD; some cases rarely may require hospitalization. Such cases however, usually occur when large doses of toxin are injected into SCM muscles on both sides located in front of the neck and/or when the injecting needle is not properly placed in SCM, but rather misplaced close to esophagus; the tube that connects the throat to stomach. In some patients' SCM is hard to find if the injector performs injections when the patient is sitting up. Having the patient lie down with the head raised helps identify better the SCM bulk and borders. Performing injections under electromyography guidance or ultrasound helps in accurate identification of the neck muscles and proper placement of the injecting needles.

Between 60–70% of the patients, with cervical dystonia express satisfaction with botulinum toxin therapy after first injection session. This percentage increases with repeat injections. In non-responders, attempts should be made to better identify and localize of the muscles. Unresponsiveness after several attempts should raise the possibility of other diagnoses including a psychogenic condition. In rare cases, unresponsiveness may be due to the development of antibodies against the botulinum toxin in the blood. Individuals who have been vaccinated against botulinum toxin may not respond to BoNT therapy. With earlier preparations of Botox (before 1997), repeated and closely spaced injections especially with large doses antibodies against Botox could be detected in 25–30%; between 5–10% of the patients became non-responsive. With the new Botox preparations that contain lower levels of

antigenic proteins, antibody formation is uncommon (close to 1%) and reported non-responsiveness is below 1% [8]. Another form of Botulinum toxin A, Xeomin (with units comparable to Botox), almost never produces antibodies due to the lack of antigenic protein in its molecule.

Focal Limb Dystonias After Limb Trauma, Stroke and Cerebral Palsy

After head injury and stroke, many patients develop dystonia in the affected, weak limbs along with increased muscle tone (spasticity). Children with spastic cerebral palsy also demonstrate dystonic hand and finger, features associated with increased muscle tone in the involved limbs. The use of botulinum toxins for treatment of these secondary dystonias is described in more detail in several chapters of this book (Chaps. 7, 8, 14).

Task Specific Dystonias

Task specific dystonias are a group of focal dystonias that usually present in the hand and forearm muscles after performing any specific fine motor movement repetitively. There is a wide range tasks that upon months or years of repetition can cause focal dystonia such as typing, palying music (piano, guitar, etc), and writing. In sports, "golfers' yip" is a kind of hand task specific dystonia observed in golfers. Foot dystonia of runners is an example of task specific dystonia in the lower limb. In runner's dystonia, the foot, the knee or the hip may demonstrate involuntary twisting and turning postures after prolonged running.

In the hand/finger dystonia, the most common form of TSD, dystonic postures occur after months or years of performing the same specific act. The wrist and fingers can flex or extend involuntarily and interfere with the patient's performance. The cause of TSD is not known but it is generally believed that it is related to a fundamental abnormality of fine motor fibers that lose their precision after frequent repetitive action, ultimately resulting in development hand and finger dystonia.

Treatment of task specific dystonia (TSD) can start with behavior modification. The results of oral medications are disappointing. In a review of literature in 2016, Drs Lungu and Ahmad concluded that botulinum toxin therapy reduces dystonic hand and finger postures and improves the patient's performance in task specific dystonia [9]. Injections into small forearm muscles are performed under electromyographic (EMG) or ultrasound (US) guidance. The latter is able to show individual forearm muscles and has more accuracy than the former (EMG) in TSD. In practice, although effective, BoNT therapy does not completely eliminate the TSD; in case of musicians dystonia, rarely, the initial level of performance is attainable.

Based on a review of literature, for writers' cramp, the total initial dose is 24 and 82 units for Botox and Dysport, respectively. This dose is applied to multiple forearm muscles identified by EMG or ultrasound. In established patients and after several injection sessions, the dose may be increased 40–45% [9].

Case Report

A 52 year-old music professor complained of difficulty with playing guitar for the past 3 years. He noted that after playing for a few minutes, the index finger of the right hand began to pull up and away from the other fingers impairing the quality of his music. Sometimes, the middle finger would do the same thing, although to a lesser extent. He complained also of a constant pain at the middle of his forearm "as if a knott were there ". Otherwise, the patient was in good health. He had played guitar since his early teens and has been a music instructor (guitar) for the past 20 years. He denied any history of trauma to that forearm. His condition has been getting worse gradually.

During an observation in the clinic and while playing guitar, the right hand's index and middle fingers involuntarily pulled up and took a dystonic posture. He complained of increased tightness of his forearm. We injected 5 units of Botox into the extensor of the index finger, (extensor indicis – Fig. 11.7) under EMG guidance. The procedure took 10 min (identifying and injecting the muscle); he tolerated the procedure well.

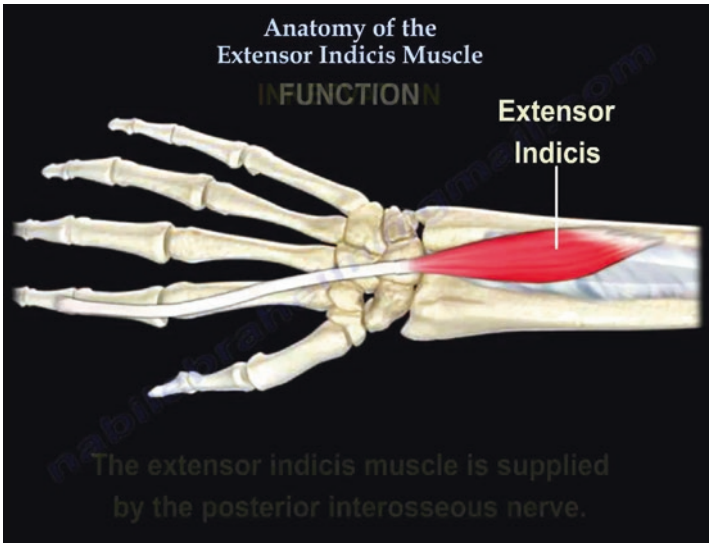

Fig. 11.7 Extensor of the index finger where Botox injection improved the patient's TSD. Courtesy Dr. Nabil Ebraheim

Two weeks after the injection, the patient visited the clinic and expressed deep satisfaction with the results. The pain in the forearm was gone and the index finger no longer pulled up; there were no side effects. He noted a 26- point increase in his performance scale rising from 100 to 126 points. The patient returned to the clinic 6 month later for a repeat treatment. A repeat injection of Botox with the same dose produced the same positive effect.

Generalized Dystonia

As briefly described earlier, generalized dystonia starts usually in childhood and many affected children have a genetic predisposition. It is possible to help patients with generalized dystonia by injecting botulinum toxins into selected, severely affected muscles. The method and dose of these local injections are not different from what is used for focal dystonias.

Tremor

Tremor is an involuntary movement that is due to rhythmic oscillation of muscles in a body part. The muscle oscillations usually alternate between two sets of muscles that have opposite function; for example muscles that bend or extend the wrist. High quality studies (comparing botulinum toxin with placebo injection) have shown significant reduction of two types of tremors after botulinum toxin injection- Parkinson tremor and essential tremor.

Parkinson Tremor

Parkinson's disease (PD) affects 1% of US population over 60 years of age [10]. Men are affected slightly more than women. The three cardinal symptoms of Parkinson's disease consist of slowness of movements (bradykinesia), muscle rigidity and hand tremor. Tremor of Parkinson's disease has the highest amplitude when the hand and forearm are at rest. In many patients with PD, this resting tremor interferes with sleeping. Approximately 20% of patients with PD have action tremor- a tremor that gets worse with moving the limb. Such tremors interfere with writing, playing musical instruments, shaving and other activities that require fine motor control.

Parkinson's disease is due to loss of dopamine in the brain and other parts of the nervous system. Dopamine is essential for maintaining the speed of movement and healthy tone of muscles. Most drugs that are used for treatment of Parkinson's disease either replenish the lost dopamine or enhance the effect of remaining dopamine.

These drugs improve slow movement and muscle stiffness (rigidity), but have less effect on Parkinson's tremor. A surgical procedure called "deep brain stimulation" by electrical stimulation of deep brain structures (basal ganglia) can markedly improve Parkinson's tremor. However, the procedure requires inserting a metal wire inside the brain and embedding a stimulator box in the muscles of the chest wall. There are also complications with surgery such as infection, minor bleeding inside the brain and malfunction of the stimulator.

Botulinum Toxin Treatment of Parkinson Tremor

Since 1996, three small open label studies (no comparison with placebo) reported that injection of botulinum toxins into the forearm muscles of patients with Parkinson's disease reduces the amplitude and frequency of Parkinson hand tremors. The drawback noted in these observations was development of hand and finger weakness (in over 30% of patients) which developed shortly after forearm injections and lasted for 2–3 months. Authors attributed this complication partly to a fixed dose injection pattern and perhaps over dosing muscles that extend the fingers.

In a three- year study that lasted from 2012 to 2015, the author and his colleagues at Yale University, conducted a study with Xeomin (a type A toxin like Botox) injection into forearm muscle of patients with Parkinson tremor [11]. Thirty- three patients were enrolled in the study and 30 patients completed it. The study was placebo controlled i.e. the effect of Xeomin injections were compared with placebo (salt water injection). It also had a flexible design i.e. in each patient, different sets of muscles were injected based on the pattern of muscles' activity seen in electromyography. Electromyography screens the electrical activity of the muscle by a special instrument. The magnitude and frequency of patients' hand tremor was measured by standard tremor scales at baseline and at 4 and 8 weeks after injection. A global impression of change assessed also the perception of patient about changes (or lack of it) in hand tremor after injections. The study was a "cross over study" i.e. the substance (placebo and Xeomin) was alternated at 3 months (second injection). For example, if patients received Xeomin the first time, the second injection was placebo and vice versa. The study was double blind meaning both the injectors and raters were not aware of what was injected (Xeomin or placebo). A nurse not involved in injections or rating of the response prepared the Xeomin or saline in a small syringe and kept a record in a password protected computer.

At the conclusion of this study, the results heavily favored Xeomin injections for treatment of Parkinson tremor. Rating assessment, both at 4 and 8 weeks after injection, demonstrated that tremor improvement was significant and different in the Xeomin group compared to the placebo group. Patients who received Xeomin also demonstrated improved quality of life and were much happier with injections than those who received placebo injections. Subtle decreased hand strength, measured by ergometer was noted in 37% of Xeomin and 22% of placebo group (not a statistically

significant difference). Hand weakness was reported by 7% of patient - considerably less than what had been reported in prior studies (30–40%). The authors concluded that a flexible pattern of injection that covers more muscles with smaller doses is effective in reducing the amplitude of PD without causing notable hand weakness in a high percentage of patients.

Essential Tremor

Essential tremor is a common genetic disorder characterized by a 4–8/second tremor observed mainly when the hands are in action. This is opposite to Parkinson's tremor which is usually observed at rest. Approximately, half of the patients have a history of a similar type of tremor in their close relatives. Severe essential tremor can significantly interfere with the activities of daily living and handicap the patient. Beta blockers (propranolol and others), primidone and topiramate are effective in reducing essential tremor, but the efficacy often wears off after chronic use. Deep brain stimulation (see under Parkinson tremor) is very effective but requires brain surgery.

Three high quality studies (comparing the effect of toxin with placebo) have investigated the utility of botulinum toxin injection into the forearm muscles for essential tremor. In 1996, Dr. Jankovic and his colleagues at Baylor Medical College in Houston, injected 50 and 100 units of Botox into the forearm muscle of 25 patients with severe essential tremor (Fig. 11.8).

After 4 weeks, 75% of the patients demonstrated 2 grade (on scale of 0–10) improvement of tremor. However, between 40–50% of the patients reported disabling weakness of fingers. These positive results were duplicated in another

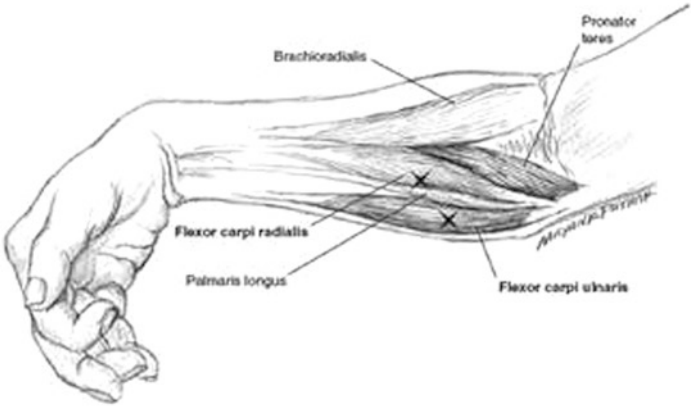

Fig. 11.8 Localization of flexor muscles of the wrist for botulinum toxin treatment of essential tremor. From Jindal and Jankovic in Manual of Botulinum Toxin Therapy. Printed with permission from Cambridge Publishing

placebo-controlled study of 123 patients with essential tremor using the same dosage of Botox. Unfortunately, a large number of patients reported notable weakness of their fingers. The investigators of both studies attributed weakness of fingers after botox injection to applying a fix dose injection approach and to the sensitivity of finger extensor muscles to Botox.

Between years 2013 to 2016, the author' group at Yale University, New Haven – CT conducted a third placebo- controlled study on essential tremor. Thirty- three patients participated and 28 completed the study. A flexible rather than fixed injection scheme was chosen for the study in that only those forearm muscles proven to be high participants in tremor received injections. Culprit muscles were identified based on EMG, registering the sound of electrical activity during tremor. Additionally, a small dose (2.5 to 5 units, half of that given in previous studies) was selected for finger extensors that have proven to be highly sensitive to Botox injections in previous studies. Patients received injections of either Xeomin (a type A toxin similar to Botox), 80–120 units or a placebo (salt water) into 6–8 forearm and two arm (biceps and triceps) muscles. The injecting doctor was blinded to what patient received (Xeomin or placebo). Standard scales were used to assess the intensity of tremor and quality of life at baseline and every 4 weeks after injection. After 4 months, the patients received a second injection alternating placebo for Xeomin or vice versa depending on what the patient had received initially. The assessments were carried out for the next 14 months, at monthly intervals. Injectors and raters were also blinded to the type and order of injections (double blind study).

Statistically significant improvement of tremor was noted after Xeomin injections along with improvement of quality of life. Patients also expressed their satisfaction with Xeomin injections (not placebo) on a patient satisfaction scale. One patient (4%) developed notable finger weakness which lasted for 2 months. This study which used a flexible injection scheme and smaller amount of toxin into forearm finger extensor muscles demonstrated efficacy of Xeomin in reducing ET tremor along with low incidence of finger weakness (4% versus 40–50% reported in previous studies).

Tics

Tics are involuntary, rapid and repetitive movements that, at times, can be stopped momentarily by will. Most tics are simple motor tics associated with no sensory or other symptoms. A more complex type of tic, presents with associated glottal sound, and sometimes vocalization (saying words or sentences) in addition to motor manifestations. Vocalizations may include profanity (coprolalia). This condition bears the name of the French physician (Tourette) who provided the first detailed description of this type of tic, and hence called Tourette syndrome. Almost all tics start in childhood and gradually improve after age 30 years (some totally disappear). However, when present and especially if they are frequent and complex, in addition to social embarrassment, they deteriorate the patients' quality of life. Many patients

with tics have premonitory signs (different sensations) or an urge to move before the emergence of tic episodes.

Treatment of tics may start with behavioral modification, for which, several programs are currently available. Pharmacological treatment of tics basically uses three groups of drugs; dopamine blockers or dopamine depleters such as flufenazine and tetrabenazine and clonidine an alpha 2 enhancer. Dopamine is a protein that is present in abundance in deep brain structures (basal ganglia). Dopamine deficiency (Parkinson's disease) or enhanced activity of dopamine (tics) are major players in manifestations of motor disorders. Some patients with disabling tics and failure to respond to oral medications, have responded to electrical stimulation of brain's deep structures (deep brain stimulation-DBS).

Dr. Jankovic and his colleagues at the Baylor College of Medicine were first to demonstrate in 10 patients that injection of Botox into the muscles involved in repetitive involuntary movements of tics can reduce the frequency and severity of the motor tics. Subsequently, in a larger study of 35 patients with tics, Botox was compared to placebo (saline injections) and authors came to the same conclusion [12]. In this study, approximately 40% of patients with recalcitrant tics, not responding to oral medications, demonstrated marked mitigation of tic movements when injected with Botox compared to placebo while many patients also lost the "urge to move" sensation they often experience before their tics. In another study, injection of very small dose of Dysport (approximately 2.5 units of Dysport equals 1 unit of Botox) into the vocal cord muscles of patients with tics and vocalization resulted in total resolution of vocal tics in 50% of the 22 patients studied. In this study, patients voice became soft in a majority of patients after vocal cord injections, but patients did not think it changed their quality of life.

Conclusion

Injection of botulinum toxins into involuntarily moving muscles can and often does reduce or stop the involuntary movements by inhibiting the release of acetylcholine at the nerve-muscle junction. Acetylcholine is a chemical that conveys the nerve's message to the muscle to activate it. Botulinum toxins are currently considered the first line of management for focal dystonias (blepharospasm, jaw, task specific and cervical dystonias) and for hemifacial spasm. The data on its use for tremors are encouraging; various studies have confirmed that botulinum toxin therapy is safe and effective and a reasonable alternative to surgery.

References

1. Hallett M. Blepharospasm: recent advances. Neurology. 2002;59:1306–12.
2. Nutt JG, Meunter MD, Aranson A, et al. Epidemiology of focal and generalized dystonia in Rochester Minnesota. Mov Disord. 1988;3:188–94.

3. Illowsky-Karp B, Alter K. Botulinum treatment of blepharospasm, orofacial/oromandibular dystonia, and hemifacial spas. Semin Neurol. 2016;36:84–91.
4. Truong D, Comella C, Fernandez HH, et al. Benign Essential Blepharospasm Study Group. Efficacy and safety of purified botulinum toxin type A (Dysport) for the treatment of benign essential blepharospasm: a randomized, placebo-controlled phase II trial. Parkinsonism Relat Disord. 2008;14:407–14.
5. Colosimo C, Bologna M, Lamberti S, et al. A comparative study of primary and secondary hemifacial spasm. Arch Neurol. 2006;63:441–4.
6. Jankovic J, Adler CH, Charles D. Primary results from cercical dystonia patient registry for observation of onabotulinum toxin A efficacy (CD Probe). J Neurol Sci. 2015;349:84–93.
7. Bledsoe IO, Comella CL. Botulinum toxin treatment of cervical dystonia. Semin Neurol. 2016;36:47–53.
8. Brin MF, Comella CL, Jankovic J. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. Mov Disord. 2008;23:1353–60.
9. Lungo C, Ahmad OF. Update on the use of botulinum toxin therapy for focal and task specific dystonias. Semin Neurol. 2016;36:41–6.
10. Jindal P, Jankovic J. Botulinum toxin treatment in Parkinson' disease and atypical Parkinsonian disorders. In: Jabbari B, editor. Botulinum toxin treatment in clinical medicine. A disease- oriented approach. Cham: Springer Publisher; 2018. p. 23–58.
11. Mittal SO, Machado D, Richardson D, Dubey D, Jabbari B. Botulinum toxin in Parkinson disease tremor: a randomized, double-blind, placebo-controlled study with a customized injection approach. Mayo Clin Proc. 2017;92:1359–67.
12. Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin in simple motor tics. A randomized, double blind, controlled clinical trial. Neurology. 2001;56:605–10.

Chapter 12
Botox in Plastic Surgery

Katherine Grunzweig and Ali Totonchi

Introduction: History of Botulinum Toxin in Plastic Surgery

The first documented use of injectable botulinum toxin in plastic surgery was in 1989 when Clark and Berris published their case in Plastic and Reconstructive Surgery regarding the use of botulinum toxin type A to treat asymmetry from rhytidectomy, where there was suspected unilateral frontal nerve paralysis in a patient [1, 2]. The first documentation of its use in humans was by Dr. Alan Scott, an ophthalmologist. His work describing the use of botulinum toxin as an alternative to strabismus surgery was published in 1980; the toxin was used in management of blepharospasm and strabismus [3, 4].

Application of the toxin for cosmetic purposes was limited in the literature until 1992 when Carruthers et al. published a paper describing its use for temporary effacement of glabellar frown lines [5]. This case series specifically evaluated the impact on rhytids from injecting purified C. botulinum A exotoxin into the glabellar region. Compared to blepharospasm treatment, cosmetic treatment of rhytids required a lower dose of toxin and did not require multiple locations into the brow and orbicularis occuli muscles. Interestingly, the authors noted a combination of collagen and C. botulinum A exotoxin to be more effective in treatment of deep glabellar frown lines- an approach that has now become a common treatment choice. Considering the novelty of this therapeutic approach, the Carruthers concluded that C. botulinum A exotoxin was not the treatment of choice for glabellar frown lines, with the caveat that it did successfully efface lines for short durations. Since then, botulinum toxin injections have become the number one non-surgical cosmetic procedure [6].

Katherine Grunzweig and Ali Totonchi are contributed equally.

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_12

A Brief FDA History: When was the Product Approved for Cosmetic Use?

The history of Food and Drug Administration's approval for use of the toxin began in 1989 with approval of Oculinum (onabotulinumtoxinA, Allergan) injections for treatment of strabismus, belpharospasm and hemifacial spasm for patients older than 12 years of age following Dr. Scott's publications [7, 8]. On label use of botox approved by the FDA includes glabellar rhytides in patients under 65. A cosmetic formulation called Botox Cosmetic was approved in 2002 for glabellar rhytids (Botox Cosmetic; Allergan, Inc., Irvine, CA). In October 2010, the FDA approved Botox for chronic migraines. In September 2013, the FDA approved onabotulinumtoxinA for lateral canthal lines ("crow's feet") [9].

Brands

The most common brands used in the United States in Plastic Surgery are Botox Cosmetic, and Dysport. While Botox (OnabotulinumtoxinA) remains the brand name created by Allergan, there are multiple botulinum toxin injectable formulations on the market. These include OnabotulinumtoxinA (Allergan: Botox, Botox Cosmetic, Vistabel, Visabex), AbobotulinumtoxinA (Medicis Pharmaceutical Corporation: Dysport, Reloxin, Azzalure), CBTX-A (not approved in U.S.; Lanzhou Institute of Biological Products: Prosigne, Lantox), BONTA (not approved in U.S.; Medy-Tox Inc.: Neuronox), IncobotulinumtoxinA (Merz Pharmaceuticals: Xeomin), TBD (Mentor Worldwide LLC: PurTox, pending U.S. trials), and Rimabotulinumtoxin B (Solstice Neurosciences Inc.: MyoBloc, NeuroBloc) [10].

Plastic Surgery Botulinum Toxin Injections in Aesthetic Practice

Botulinum toxin use in plastic surgery is generally focused on two areas: facial musculature chemodenervation and migraine. Glabellar injections, the first procedure approved by the FDA, were reported as early as 1989 in plastic surgery literature. There are more than 2800 clinical and nonclinical articles between 1986–2013, and more than 400 peer-reviewed articles on the use of Botox [6].

After research published on glabellar frown lines and corrugator injections, other facial cosmetic injections grew in popularity. The late 1990s sustained a significant growth in publications regarding use of botulinum toxin injections in the face. Aesthetic use of botulinum toxin to improve rhytids and improve upon facial symmetry has grown. In 1998, Foster et al. wrote one of the first review articles on cosmetic application of botulinum toxin, and noted that it was already in use for

glabellar folds, lateral periocular rhytids, lower eyelid orbicularis rides, brow ptosis, central forehead wrinkles, perioral lipstick lines, and platsymal bands in the neck [11].

Literature regarding cosmetic uses of botulinum toxin can be found in the fields of dermatology, ophthalmology and plastic surgery. Glabellar injections grew as an independent procedure, especially after publication of the case series by Carruthers et al. in 1992 [5]. Glabellar injections underwent a formal double blind placebo controlled study of botulinum toxin type A in 2002 and in 2003, establishing efficacy, safety and cosmetic improvement in rhytids [12, 13].

In 1997, in the Annals of Plastic Surgery, Guerrissi et al. documented the use of botulinum toxin injections in corrugator, frontalis and orbicularis oculi muscles to improve facial mimetic wrinkles [14]. Frontalis injections appeared in the literature in 1997 in both Laryngoscope and Annals of Plastic Surgery, and resurfaced in 2003 documenting an associated improvement in migraine symptoms (discussed below) [14, 15]. Orbicularis injections of lower eyelids also grew in popularity as an injection site, to treat hypertrophic muscle [8]. Botulinum toxin mediated brow lifts became popular around the same time, to affect mid-lateral brow elevation [8, 16].

Lateral canthal lines ("Crow's Feet") first appear in the literature as injection sites in 1997 in the Journal of Otolaryngology, and shortly after Dr. Fagien described the use of botulinum toxin for the region in 1999 in Plastic and Reconstructive Surgery [8, 17]. Further publications on lateral canthal lines increased in the mid to late 2000s, with further refinement regarding volume and injection sites in 2016 [9].

Nasolabial fold modification, achieved by zygomaticus major and minor injections, was also introduced in the 1990s. Although effacement of the fold is primarily accomplished by fillers, patients with short upper lips are considered as ideal candidates for use of botulinum toxin injections to efface the nasolabial fold [18]. In 2003, Dr. Kane published a retrospective study of over 1000 injections (starting in 1993) of the nasolabial region in Plastic and Reconstructive Surgery; in a 1999 publication, Dr. Fagien further discussed injection subtleties also in the plastic surgery literature [8, 19]. Perioral lines, with injections adjacent to fine vertical rhytids over orbicularis close to vermillion ridge, (initially noted in 2003 by Carruthers et al.) was discussed in the 2004 consensus recommendations on botulinum toxin and cosmetic use [20, 21].

Treatment of chin projection, rhytids, and peau d'orange wrinkling from the mentalis has been addressed more recently in the literature, first appearing in 2005 as a double blind placebo controlled study, and subsequently in Plastic and Reconstructive Surgery in 2015 [22, 23]. Depressor Anguli Oris (melomental) injections also appear as part of the review of lower facial improvement, in the French Consensus in 2011 [24].

Use for contouring the lower face, particularly masseter hypertrophy and in patients with bruxism, was first published in the basic science literature in 1993, and as a case report in 1998, before multiple articles were published by various disciplines in 2005–2006; the role of botulinum toxin-A in facial sculpting was further discussed in Facial Plastic Surgery Clinics of North America in 2010 [25–29]. Treatment of platysmal bands with botulinum toxin appeared in Plastic and Reconstructive Surgery in 1999 [30].

Plastic surgery and the cosmetic use of botulinum toxin in facial rejuvenation and contour modification was reviewed in the 2014 Global Consensus on OnabotulinumtoxinA: injections and targets [6]. As reviewed in this chapter, injection sites and indications in the upper face included glabellar lines, horizontal forehead lines, lateral canthal lines, and brow elevation, with trends towards lower dosage to neuromodulate rather than completely denervate the muscles. Midface rhytids, including infraorbital rhytids, nasal oblique lines, nasal flare, nasal tip elevation (nasalis injection) and appearance of excessive gingiva were also discussed by the expert panel as indicated locations for injections. Within the lower face, the Global Consensus discussed depressor anguli oris overactivity, mentalis overactivity, masseter overactivity, perioral rhytids, platysmal bands as common sites for onabotulinumtoxinA injection.

Use as an adjunct to filler was described early on in the Carruthers' first paper, subsequently by Dr. Fagien, and most recently by de Maio et al. as part of the Facial Aesthetics Consensus Committee in 2017 [5, 8, 31]. Injectable fillers are the second leading procedure behind botulinum toxin injections, and the combination of the two can be used for temple volumization, eyebrow shaping, and forehead contouring.

The late 1990s also saw introduction of pre-treatment of recurrent rhytids in lower lids and canthus with botulinum toxin before CO2 laser, to assist in effacing deep-set rhytids before resurfacing [8, 32]. This has not received significant attention in current literature.

Hyperhidrosis spans multiple specialties as does intervention using botulinum toxin injections. Use of botulinum toxin for management of hyperhidrosis was described first in dermatology in 1996, in laryngology for Frey's Syndrome in 1997, and then published in the Aesthetic Surgery journal in 2003 [33–35].

Plastic Surgery Botulinum Toxin Injections for Congenital and Traumatic Facial Asymmetry

Clark et al., as previously noted, first published the use of botulinum toxin injections for treatment of facial asymmetry in 1989 after unilateral nerve injury from rhytidectomy [3]. Unilateral nerve injury treated with botulinum toxin injections has also been documented for marginal mandibular nerve paralysis: asymmetry of the lower lip due to absence of depressor function can be treated by injecting the contralateral depressor labii inferioris with botulinum toxin [36].

Facial paralysis is another disorder where botulinum toxin has been employed to achieve symmetry with the contralateral side. De Maio et al. published an expert opinion in 2008 regarding the use of botulinum toxin in facial palsy and autonomic disorders, noting that injection on the hyperkinetic side assists in restoring facial symmetry as well as alleviating pain [37].

Hemifacial spasm also can be treated with botulinum toxin, as noted by Chundury et al. in 2016 [38]. As discussed above, masseter hypertrophy can also be treated in

the same fashion. Use of botulinum toxin for facial synkinesis after facial nerve palsy, as well as injections for platsymal synkinesis, have also become very common as a modality to achieve symmetry [8, 39–42]. Most recently, in 2017, a comparison of available botulinum toxins for treatment of facial synkinesis concluded that incobotulinumtoxinA may be less efficacious than onabotulinumA [43].

A Brief Review: Migraines

Botox use in chronic migraine in adults was approved in 2010 by the FDA [44]. BotulinumtoxinA is currently used in the assessment of migraine trigger sites in the preoperative work-up for migraine surgery, though its efficacy was initially considered controversial [45–49]. Trigger sites are injected 1–3 months apart to assess response, and those sites with 50% or more improvement in symptoms indicate potential sites for migraine surgery.

Research to date also suggests that botulinum toxin can be used in isolation without surgery in candidates who do not desire to undergo surgery or who are unable to do so [50]. Pediatric populations have also benefited from botulinum toxin for migraines – for chronic daily headache, without surgical intervention, with research dating more recently from 2009–2012 [51–53].

Plastic Surgery Botulinum Toxin Injections for Hand Therapy

The injection of botulinum toxin to treat hand tremors and dystonia was primarily performed by neurology and movement disorder specialists in the 1990s [54, 55]. As previously noted, use for palmar hyperhidrosis grew in popularity as well.

The use of botulinum toxin-A for management of vasospastic disorders was initially published in the plastic surgery literature in 2007 [56]. The application of botulinum toxin in management of vasospastic disorders has expanded recently, following publications in 2014–2015 that discussed the use, indications and comparison of botulinum toxins in management of vasospasm, chronic regional pain syndrome, and as an adjunct to hand therapy [57, 58].

Plastic Surgery Botulinum Toxin Injections in Pediatric Surgery

Botox use in children is often cited for migraine, hyperhidrosis, torticollis, cleft lip, spasticity and muscular hypertrophy (Fu et al.); the use of Botox increased in the early 2000s [44]. In 2006, it was written that cleft lip repair with botulinum

toxin injections in orbicularis oris before cheiloplasty decreases tension on the surgical wound and further elucidated upon in 2009 and 2014 [59–61]. Torticollis treated with botulinumtoxinA injections in the sternocleidomastoid or upper trapezius improved neck range of motion in older pediatric patients in the mid-2000's [62–64]. Just as in adults, botulinum toxin can be used in axillary and palmar hyperhidrosis [65–67]. Masseter hypertrophy is less commonly treated in pediatrics [68, 69].

Conclusion

The use of botulinum toxin injections in plastic surgery reveals an explosive growth from the early 1990s into the mid-2000s, with further developments and refinements in volume, injection pattern, and adjuncts occurring in the most recent decade. From the early beginnings in ophthalmology, plastic surgery injection of botulinum toxin for chemodenervation for aesthetic restoration, improvement in symmetry due to nerve damage or trauma, alleviation of migraines and assessment for surgery, and in pediatric plastic surgery has closely relied on collaboration and co-education among closely related specialties.

References

1. Clark RP, Berris CE. Botulinum toxin: a treatment for facial asymmetry caused by facial nerve paralysis. Plast Reconstr Surg. 1989;84(2):353–5.
2. Rohrich RJ, Janis JE, Fagien S, Stuzin JM. The cosmetic use of botulinum toxin. Plast Reconstr Surg. 2003;112(5 Suppl):177S–88S. quiz 188S, 192S; discussion 189S–191S
3. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. Ophthalmology. 1980;87(10):1044–9.
4. Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. Investig Ophthalmol. 1973;12(12):924–7.
5. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. J Dermatol Surg Oncol. 1992;18(1):17–21.
6. Sundaram H, Signorini M, Liew S, et al. Global aesthetics consensus: botulinum toxin type A–evidence-based review, emerging concepts, and consensus recommendations for aesthetic use, including updates on complications. Plast Reconstr Surg. 2016;137(3):518e–29e.
7. Jabbari B. History of botulinum toxin treatment in movement disorders. Tremor Other Hyperkinet Mov (N Y). 2016;6:394.
8. Fagien S. Botox for the treatment of dynamic and hyperkinetic facial lines and furrows: adjunctive use in facial aesthetic surgery. Plast Reconstr Surg. 1999;103(2):701–13.
9. Carruthers A, Bruce S, Cox SE, Kane MA, Lee E, Gallagher CJ. OnabotulinumtoxinA for treatment of moderate to severe crow's feet lines: a review. Aesthet Surg J. 2016;36(5):591–7.
10. Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. J Clin Aesthet Dermatol. 2014;7(2):31–9.
11. Foster JA, Wulc AE, Holck DE. Cosmetic indications for botulinum A toxin. Semin Ophthalmol. 1998;13(3):142–8.

12. Carruthers JA, Lowe NJ, Menter MA, et al. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. J Am Acad Dermatol. 2002;46(6):840–9.
13. Carruthers JD, Lowe NJ, Menter MA, Gibson J, Eadie N. Botox glabellar lines IISG. Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. Plast Reconstr Surg. 2003;112(4):1089–98.
14. Guerrissi J, Sarkissian P. Local injection into mimetic muscles of botulinum toxin A for the treatment of facial lines. Ann Plast Surg. 1997;39(5):447–53.
15. Koch RJ, Troell RJ, Goode RL. Contemporary management of the aging brow and forehead. Laryngoscope. 1997;107(6):710–5.
16. Frankel AS, Kamer FM. Chemical browlift. Arch Otolaryngol Head Neck Surg. 1998;124(3):321–3.
17. Ellis DA, Tan AK. Cosmetic upper-facial rejuvenation with botulinum. J Otolaryngol. 1997;26(2):92–6.
18. Dayan SH, Maas CS. Botulinum toxins for facial wrinkles: beyond glabellar lines. Facial Plast Surg Clin North Am. 2007;15(1):41–9. vi
19. Kane MA. The effect of botulinum toxin injections on the nasolabial fold. Plast Reconstr Surg. 2003;112(5 Suppl):66S–72S. discussion 73S–74S
20. Carruthers J, Carruthers A. Aesthetic botulinum A toxin in the mid and lower face and neck. Dermatol Surg. 2003;29(5):468–76.
21. Carruthers J, Fagien S, Matarasso SL. Botox consensus G. Consensus recommendations on the use of botulinum toxin type A in facial aesthetics. Plast Reconstr Surg. 2004;114(6 Suppl):1S–22S.
22. Beer K, Yohn M, Closter J. A double-blinded, placebo-controlled study of Botox for the treatment of subjects with chin rhytids. J Drugs Dermatol. 2005;4(4):417–22.
23. Wu DC, Fabi SG, Goldman MP. Neurotoxins: current concepts in cosmetic use on the face and neck--lower face. Plast Reconstr Surg. 2015;136(5 Suppl):76S–9S.
24. Raspaldo H, Niforos FR, Gassia V, et al. Lower-face and neck antiaging treatment and prevention using onabotulinumtoxin A: the 2010 multidisciplinary French consensus–part 2. J Cosmet Dermatol. 2011;10(2):131–49.
25. Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E. Botulinum A toxin effects on rat jaw muscle spindles. Acta Otolaryngol. 1993;113(3):400–4.
26. Rijsdijk BA, van ER, Zonneveld FW, Steenks MH, Koole R. Botulinum toxin type A treatment of cosmetically disturbing masseteric hypertrophy. Ned Tijdschr Geneeskd. 1998;142(10):529–32.
27. Park MY, Ahn KY, Jung DS. Botulinum toxin type A treatment for contouring of the lower face. Dermatol Surg. 2003;29(5):477–83. discussion 483
28. Choe SW, Cho WI, Lee CK, Seo SJ. Effects of botulinum toxin type A on contouring of the lower face. Dermatol Surg. 2005;31(5):502–7. discussion 507-508
29. Wu WT. Botox facial slimming/facial sculpting: the role of botulinum toxin-A in the treatment of hypertrophic masseteric muscle and parotid enlargement to narrow the lower facial width. Facial Plast Surg Clin North Am. 2010;18(1):133–40.
30. Matarasso A, Matarasso SL, Brandt FS, Bellman B. Botulinum A exotoxin for the management of platysma bands. Plast Reconstr Surg. 1999;103(2):645–52. discussion 653–645
31. de Maio M, Swift A, Signorini M, Fagien S. Aesthetic leaders in facial aesthetics consensus C. Facial assessment and injection guide for botulinum toxin and injectable hyaluronic acid fillers: focus on the upper face. Plast Reconstr Surg. 2017;140(2):265e–76e.
32. West TB, Alster TS. Effect of botulinum toxin type A on movement-associated rhytides following CO2 laser resurfacing. Dermatol Surg. 1999;25(4):259–61.
33. Bushara KO, Park DM, Jones JC, Schutta HS. Botulinum toxin--a possible new treatment for axillary hyperhidrosis. Clin Exp Dermatol. 1996;21(4):276–8.
34. Bjerkhoel A, Trobbe O. Frey's syndrome: treatment with botulinum toxin. J Laryngol Otol. 1997;111(9):839–44.

35. Centeno RF. Botulinum toxin A for managing focal hyperhidrosis. Aesthet Surg J. 2003;23(1):67–9.
36. Hussain G, Manktelow RT, Tomat LR. Depressor labii inferioris resection: an effective treatment for marginal mandibular nerve paralysis. Br J Plast Surg. 2004;57(6):502–10.
37. de Maio M. Therapeutic uses of botulinum toxin: from facial palsy to autonomic disorders. Expert Opin Biol Ther. 2008;8(6):791–8.
38. Chundury RV, D'Angelo AS, Couch SM, Holds JB. Subjective and objective measures in the treatment of Hemifacial spasm with onabotulinumtoxinA. Ophthal Plast Reconstr Surg. 2016;32(2):133–7.
39. Choi KH, Rho SH, Lee JM, Jeon JH, Park SY, Kim J. Botulinum toxin injection of both sides of the face to treat post-paralytic facial synkinesis. J Plast Reconstr Aesthet Surg. 2013;66(8):1058–63.
40. Couch SM, Chundury RV, Holds JB. Subjective and objective outcome measures in the treatment of facial nerve synkinesis with onabotulinumtoxinA (Botox). Ophthal Plast Reconstr Surg. 2014;30(3):246–50.
41. Dall'Angelo A, Mandrini S, Sala V, et al. Platysma synkinesis in facial palsy and botulinum toxin type A. Laryngoscope. 2014;124(11):2513–7.
42. Chuang DC, Chang TN, Lu JC. Postparalysis facial synkinesis: clinical classification and surgical strategies. Plast Reconstr Surg Glob Open. 2015;3(3):e320.
43. Thomas AJ, Larson MO, Braden S, Cannon RB, Ward PD. Effect of 3 commercially available botulinum toxin neuromodulators on facial Synkinesis: a randomized clinical trial. JAMA Facial Plast Surg. 2017;20:141–7.
44. Fu KJ, Teichgraeber JF, Greives MR. Botulinum toxin use in pediatric plastic surgery. Ann Plast Surg. 2016;77(5):577–82.
45. Achauer BM, Eriksson E, Vander Kolk C, Coleman JJ, Russell RC, Guyuron B. Plastic surgery: indications, operations, and outcomes. St. Louis: Mosby; 2000.
46. Evers S. Status on the use of botulinum toxin for headache disorders. Curr Opin Neurol. 2006;19(3):310–5.
47. Smuts JA, Schultz D, Barnard A. Mechanism of action of botulinum toxin type A in migraine prevention: a pilot study. Headache. 2004;44(8):801–5.
48. Welch KM. Botulinum toxin type A for the treatment of headache: con. Headache. 2004;44(8):831–3.
49. Blumenfeld A. Botulinum toxin type A for the treatment of headache: pro. Headache. 2004;44(8):825–30.
50. Cho SJ, Song TJ, Chu MK. Treatment update of chronic migraine. Curr Pain Headache Rep. 2017;21(6):26.
51. Ahmed K, Oas KH, Mack KJ, Garza I. Experience with botulinum toxin type A in medically intractable pediatric chronic daily headache. Pediatr Neurol. 2010;43(5):316–9.
52. Chan VW, McCabe EJ, MacGregor DL. Botox treatment for migraine and chronic daily headache in adolescents. J Neurosci Nurs. 2009;41(5):235–43.
53. Kabbouche M, O'Brien H, Hershey AD. OnabotulinumtoxinA in pediatric chronic daily headache. Curr Neurol Neurosci Rep. 2012;12(2):114–7.
54. Jankovic J, Schwartz K. Botulinum toxin treatment of tremors. Neurology. 1991;41(8):1185–8.
55. Bhakta BB, Cozens JA, Bamford JM, Chamberlain MA. Use of botulinum toxin in stroke patients with severe upper limb spasticity. J Neurol Neurosurg Psychiatry. 1996;61(1):30–5.
56. Van Beek AL, Lim PK, Gear AJ, Pritzker MR. Management of vasospastic disorders with botulinum toxin A. Plast Reconstr Surg. 2007;119(1):217–26.
57. Neumeister MW. The role of botulinum toxin in vasospastic disorders of the hand. Hand Clin. 2015;31(1):23–37.
58. Kalliainen LK, O'Brien VH. Current uses of botulinum toxin A as an adjunct to hand therapy interventions of hand conditions. J Hand Ther. 2014;27(2):85–94. quiz 95
59. Tollefson TT, Senders CM, Sykes JM, Byorth PJ. Botulinum toxin to improve results in cleft lip repair. Arch Facial Plast Surg. 2006;8(3):221–2.

60. Galarraga IM. Use of botulinum toxin in cheiloplasty: a new method to decrease tension. Can J Plast Surg. 2009;17(3):e1–2.
61. Chang CS, Wallace CG, Hsiao YC, Chang CJ, Chen PK. Botulinum toxin to improve results in cleft lip repair. Plast Reconstr Surg. 2014;134(3):511–6.
62. Oleszek JL, Chang N, Apkon SD, Wilson PE. Botulinum toxin type A in the treatment of children with congenital muscular torticollis. Am J Phys Med Rehabil. 2005;84(10):813–6.
63. Joyce MB, de Chalain TM. Treatment of recalcitrant idiopathic muscular torticollis in infants with botulinum toxin type A. J Craniofac Surg. 2005;16(2):321–7.
64. Collins A, Jankovic J. Botulinum toxin injection for congenital muscular torticollis presenting in children and adults. Neurology. 2006;67(6):1083–5.
65. Bhakta BB, Roussounnis SH. Treating childhood hyperhidrosis with botulinum toxin type A. Arch Dis Child. 2002;86(1):68.
66. Vazquez-Lopez ME, Pego-Reigosa R. Palmar hyperhidrosis in a 13-year-old boy: treatment with botulinum toxin A. Clin Pediatr (Phila). 2005;44(6):549–51.
67. Coutinho dos Santos LH, Gomes AM, Giraldi S, Abagge KT, Marinoni LP. Palmar hyperhidrosis: long-term follow-up of nine children and adolescents treated with botulinum toxin type A. Pediatr Dermatol. 2009;26(4):439–44.
68. Castro WH, Gomez RS, da Silva Oliveira J, Moura MD, Gomez RS. Botulinum toxin type A in the management of masseter muscle hypertrophy. J Oral Maxillofac Surg. 2005;63(1):20–4.
69. von Lindern JJ, Niederhagen B, Appel T, Berge S, Reich RH. Type A botulinum toxin for the treatment of hypertrophy of the masseter and temporal muscles: an alternative treatment. Plast Reconstr Surg. 2001;107(2):327–32.

Chapter 13
Botulinum Toxin Therapy for Autonomic Dysfunction (Excessive Drooling and Excessive Sweating) and for Skin Disorders

Introduction

Salivary glands that secret saliva, and sweat glands receive their innervation from the sympathetic and parasympathetic nervous systems. Sympathetic and parasympathetic nervous systems are part of the autonomic nervous system. Autonomic nervous system is a part of nervous system that, unlike the motor system, is not under voluntary control. Saliva and sweat secret in response to peripheral stimuli independent of the individuals' wish and will. Sympathetic nervous system excites the salivary and sweat glands. Sympathetic nerves also innervate important muscles in the body such as heart and intestine. Stimulation of the sympathetic nerves increases the number of heart beats while slowing down movements of the gut. Parasympathetic nervous system is another major part of autonomic nervous system that opposes the function of the sympathetic nervous system (for example it slows heart beat or increases movements of the gut). Sympathetic and parasympathetic nerves are much thinner than motor and sensory nerves and are devoid from the fatty myelin sheet; this sheet covers motor and sensory nerves and enhances their conduction. Like motor nerves, sympathetic nerves also use a chemical agent at their endings that activates their targets (salivary or sweat glands). This chemical neurotransmitter, like that of the motor nerves, is acetylcholine.

Botulinum neurotoxins (BoNT) which are produced by a bacteria (clostridium botulinum), were purified and prepared for medical use between 1940–1970 (see Chap. 1 of this book on the history of botulinum toxins). The toxin molecule travels to the nerve endings after intramuscular or skin injection. There, through a cascade of complicated mechanisms (see Chap. 2 of this book), it blocks the release of acetylcholine from the nerve endings. This function of botulinum toxin has made it a useful commodity for treatment of a variety movement disorders, characterized by involuntary movements. Blocking acetylcholine release also decreases the muscle tone, and hence, helps spastic muscles to relax. This is another major indication of botulinum toxins that already have received approval for use in stroke, multiple

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_13

sclerosis and cerebral palsy; intramuscular injection of BoNT can relax tense and often painful spastic muscles. Since sympathetic nerve endings also use acetylcholine as the chemical neurotransmitter to activate salivary and sweat glands, injection of BoNT into these glands can reduce secretion of saliva and sweat when excessive salivation and sweating become problematic.

Anatomy and Physiology of Salivary Glands

Three glands (parotid, submandibular, and sublingual) are the major producers of saliva (Fig. 13.1). Saliva plays an important role in lubrication, digestion, immunity and maintenance of homeostasis in the human body. The parotid gland is located under the skin in front of lower part of the ear and extends to the angle of the jaw. It is divided by the facial nerve into a superficial lobe and a deep lobe. The submandibular gland, the second largest salivary gland after the parotid, is located in the submandibular (under jaw bone) triangle. The sublingual (under the tongue) gland is the smallest of the three and lies in the anterior floor of the mouth below the tongue (Fig. 13.1).

Each gland produces high volumes of saliva relative to its mass. Since parotid gland is the largest (14–28 grams), most saliva is produced by this gland. Production of saliva is not controlled by an individual's will, but rather, controlled by autonomic nervous system, sympathetic and parasympathetic nerve fibers. In stimulated state, i.e chewing, parotids glands provide most of the saliva. In the unstimulated state, however, 70% of saliva is secreted by the submandibular (weighs 10–15 grams) and sublingual glands. The flow of saliva is five times greater in the stimulated state than in the resting state.

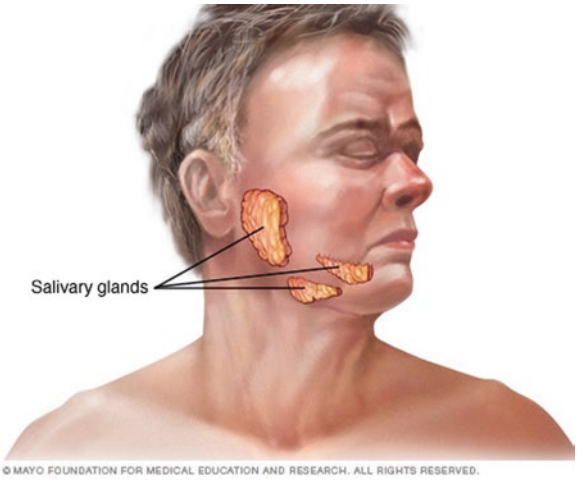

Fig. 13.1 Location of the three major salivary glands: parotid, Submandibular (*under jaw bone*) and sublingual(*under the tongue*) glands. Printed with permission from Mayo Foundation

Sialorrhea or drooling is a debilitating condition which implies presence of excess saliva in the mouth beyond the lip margin. Drooling is common in babies but subsides between the ages 15 to 36 months with establishment of salivary continence. Drooling is considered abnormal if it persists beyond 4 years of age.

Pathologic drooling can be due to increased production of saliva (usually due to certain drugs) or related to disease conditions that disrupt mechanisms that clear and remove saliva from the mouth. These diseases cause retainment of saliva in the mouth and drooling by weakening the tongue or impairing the swallowing reflexes. Drooling frequently occurs in neurological diseases such as Parkinson's disease (PD), amyotrophic lateral sclerosis (Lou Gehrig's disease -ALS) and in children with cerebral palsy (CP). In adults, PD is the most common cause [4] of drooling affecting 70%–80% the patients. In children, the most common cause of drooling is cerebral palsy with a quoted incidence of 10–38%. Drooling due to increased production of saliva is seen in 30%–80% of schizophrenic patients who are treated with clozapine. Regardless of the cause, excessive drooling can lead to social embarrassment, aspiration, skin breakout, bad odor, and sometimes local infection.

Sialorrhea is difficult to treat. Management can be conservative or invasive. Conservative treatments include changes in diet or habits of eating, oral-motor exercises, intra-oral devices such as palatal training devices, and oral medications. Behavioral modification has been advocated by some, but results have been inconsistent. Severe cases of drooling non-responsive to medications may require removal of salivary gland (s) by surgery or local radiation of the salivary glands. Surgical approach offers more permanent results, but it is an invasive process that is not without side effects. Local radiation of the glands is now hardly practiced.

The main category of drugs used for reduction of drooling is anticholinergic medications. These medications block the effect of acetylcholine that activates the glands to secret saliva. Several anticholinergic drugs are available in the market under the trade names of glycopyrrolate, benztropine, scopalamine and tropicamide. Glycopyrrolate oral solution is the first drug approved in the United States for treatment of drooling in children who have neurologic conditions. Elderly patients tolerate oral anticholinergic agents poorly due to side effects such as confusion and blurring of vision. Glycopyrrolate is a favorite of many physicians since presence of a quaternary ammonium in its molecule prevents its passage through blood-brain barrier in large amounts, ultimately decreasing the occurrence of central side effects. It is effective and safe at a dose of 1 mg, three times a day. In one high quality study (comparing the drug with placebo), application of intraoral tropicamide films (1 mg), was shown to decrease saliva volume in non-demented parkinson patients. Medications that are used for relieving heartburn and reflux have also been suggested for treatment of drooling; however, their effectiveness in managing drooling has not been shown in any high quality studies (comparing the drug with placebo).

Botulinum Neurotoxin (BoNT) Therapy for Excessive Drooling (Sialorrhea)

Two forms of botulinum toxin(types A and B) are approved for clinical practice out of 7 discovered toxin types. Three type A toxins are marketed in US under the trade names of Botox, Xeomin and Dysport. The type B toxin is called Myobloc (Neurobloc in Europe) see (Chap. 3 for description on marketed BoNTs). Due to inherent molecular differences among these toxins, the projected equivalency value of these BoNTs is only an approximation; 1 unit of Botox = 1 unit of Xeomin = 2.5–3 units of Dysport = 40–50 units of Myobloc.

The first study (open label, no placebo used for comparison) indicating efficacy of BoNTs in reducing excessive saliva in 9 patients with Parkinson's disease was published in the year 2000. All patients demonstrated reduction of saliva after injection of Botox into the parotid gland. None reported any side effects. Since then, the efficacy and safety of BoNTs in management of sialorrhea was assessed by 9 high quality studies (comparing toxin injection with placebo) both in adults and in children. Six of these studies were conducted with the type B toxin. These studies have found objective evidence (measured by reduction in the saliva volume) after BoNT injection into the glands. This was associated, in most patients, with expression of satisfaction and improvement of their quality of life. In adults, side effects were infrequent and minor consisting of slight local pain at the time of injection, minor local bleeding and subtle-transient swallowing difficulty. Patients with drooling in Parkinson's disease responded better than other patients. The effect lasted 3–6 months. It has been shown that the composition of the saliva does not change after BoNT injections. One study compared the effect of type A and type B toxins in sialorrhea and found earlier onset with type B toxin, but equal efficacy. Another study found equal efficacy between two type A toxins (Botox and Xeomin). In children with cerebral palsy the results were equally impressive and side effects were infrequent and subtle: however, one study reported development of swallowing difficulties (transient) in several children.

Technique of Injection

A small narrow syringe (1 cc) with 10 divisions of 0.1 cc and a short, thin needle (½ to ¾ inch, gauge 30) is used for injection of the toxin into the glands. Although many physicians inject parotid gland only, injection of both parotid and submaxillary glands is advisable for achieving best results. Many physicians, perform injections merely based on the anatomical knowledge of the parotid and sumaxillary gland locations without the use of ancillary techniques. (Fig. 13.2).

The number of injection per gland varies among different physicians. Most physicians recommend injecting into more than one site for the parotid gland.

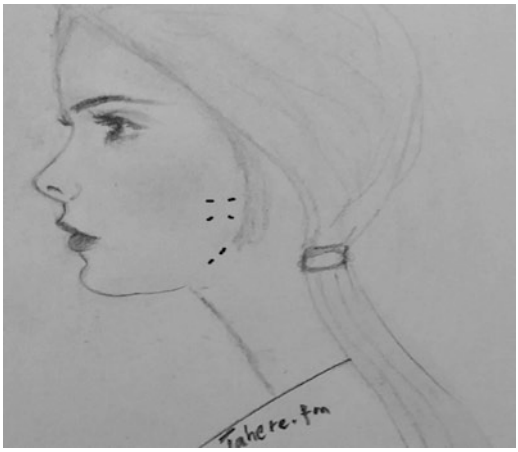

Fig. 13.2 Author's injection technique using 4 injection sites for the parotid gland and 2 injection sites for the submaxillary gland (located below the jaw bone close to angle of the jaw). Drawing courtesy of Dr.Tahereh Mousavi

A more precise way to perform parotid and submaxillary injections for drooling is via the use of ultrasound. Under ultrasound guidance, it is possible to visualize the gland, see the tip of the needle as it is approaching and entering into the gland as well as visualization of the injected material into the gland. In adults, usually, no local anaesthesia is necessary before injections. The glands are under the skin and easily accessible. In children, local application of a numbing cream such as Emla cream and/or application of a numbing skin spray seconds before each injection is helpful.

Excessive Sweating (Hyperhidrosis)

Hyperhidrosis (excessive sweating) is a debilitating condition that can lead to emotional and social embarrassment. In severe cases, it can cause occupational, physical and psychological disability. One epidemiologic survey in 2004 estimated that as many as 0.5% of the US population may be suffering from the debilitating effects of hyperhidrosis with major interference in daily activities.

Hyperhidrosis can be classified into primary and secondary hyperhidrosis. Primary hyperhidrosis has an incidence of 06–1% in general population [3]. Many cases of childhood hyperhidrosis are hereditary with more than one member of the family being affected. A genetically dominant form of excessive sweating with the onset in childhood is now recognized with a defined abnormality of chromosome 14.

The diagnostic criteria for primary hyperhidrosis include excessive sweating for at least 6 months, no obvious cause and least two of the following features: sweating occurring at least once per week, sweating impairing daily activities, a bilateral and relatively symmetric pattern of sweating, an age of onset younger than 25, positive family history and cessation of focal sweating during sleep.

Secondary hyperhidrosis can be caused by certain drugs (for example sertraline), induced by toxins (acrylamide)], caused by a systemic illness (endocrine and metabolic disorders, tumors, spinal cord lesions). Certain congenital disorders that involve the autonomic nervous system such as familial dysautonomia (Riley-Day syndrome) are also often associated with excessive sweating. . Among the other causes of secondary hyperhidrosis is compensatory hyperhidrosis. In this condition, there is increased sweating in parts of the body below the level of a surgery called sympathectomy. Gustatory hyperhidrosis is a familial disorder in which, the face sweats during eating. Gustatory hyperhidrosis is sometimes the results of trauma to the face or neck.

The glands that secret sweat are called eccrine glands. Eccrine glands have the highest concentration in the region of armpit (axilla), palms and sole of the feet; hence these are the primary areas involved in excessive sweating. Excessive sweating of the face and scalp is less common. Sympathetic nervous system, a division of autonomic nervous system, stimulates sweat glands. As mentioned earlier this chapter, the nerves of autonomic nervous system (sympathetic or parasympathetic) are very thin fibers with slow conduction (compared to motor nerves) and function independent of individual's will. Sympathetic nerves use acetylcholine at their end as the chemical transmitter that excites the sweat glands.

Anatomy and Physiology of Sweating

The pathway for control of sweating (sudomotor pathway) starts in the cortex, the 3–4 mm superficial layer of the brain that contains millions of nerve cells**.** From cortex, the fibers travel down to lower centers of the nervous system which exert autonomic control such as hypothalamus and medulla (elongated lower part of the brain before spinal cord). The sweat fibers cross in medulla and travel on the other side of the spinal cord. Emerging from the lateral part of the spinal cord, sympathetic nerves involved in secretion of sweat enter sympathetic ganglia. Sympathetic ganglia are, a group of sympathetic nerve cells send fibers to the sweat glands. These fibers are thin sympathetic fibers with acetylcholine at their end as chemical activator of the sweat gland. A lesion anywhere in this pathway, can interrupt the secretion of sweat.

Sweat glands in the palms and soles are mostly activated by emotional stimuli. Primary hyperhidrosis which is usually familial and absent during sleep, most likely results from abnormal function of the areas of the brain responsible for emotional sweating such as hypothalamus. Sweating also happens during exposure to external heat. It is believed this form sweating which has a more diffuse distribution (including face and scalp) has a different anatomic pathway in the brain.

Treatment of Excessive Sweating (Hyperhidrosis)

Treatment strategies to control excessive sweating include application of topical agents on the skin, administration of oral medications, a procedure called iontophoresis and local injection of botulinum toxins into the sweated areas:

Aluminum salts are the main topical agents used for treatment of hyperhidrosis. Their mechanism of action is not clear but, is attributed to either an interaction between aluminum chloride and keratin in the sweat ducts leading to sweat duct closure or to a direct action on the excretory eccrine gland epithelium (lining cells of the sweat gland). Aluminum salts are only effective for mild cases of hyperhidrosis; their duration of effect is often limited to 48 hours. Skin irritation, probably related to high salt concentration is the main side effect of aluminum salt treatment.

Glycopyrrolate 1–2 mg twice a day, oxybutynin 5–7.5 mg twice a day [20], and methantheline bromide 50 mg twice a day are commonly used anticholinergic agents for pharmacological management of hyperhidrosis. Side effects, especially in elderly, can be disabling to include dry mouth, blurring of vision, urinary hesitancy, dizziness, tachycardia, and confusion. Clonidine, given as 0.1 mg twice a day, is also partially effective by inhibiting the sympathetic output. Side effects include dry mouth, dizziness, constipation, sedation and a fall in blood pressure.

Iontophoresis is a procedure that introduces an ionized substance through application of a direct electrical current on intact skin. Tap water and anticholinergic agents (glycopyrrolate) are usually used for iontophoresis. Tap water iontophoresis must be performed initially every two-three days until therapeutic effect is achieved. Once therapeutic effect is achieved for two weeks, treatment can be done once every two to three weeks. Duration of the effect for both tap water and anticholinergic iontophoresis is only a few days which makes iontophoresis an undesirable mode of treatment of hyperhidrosis.

Botulinum Toxin Treatment of Hyperhidrosis

Injection of botulinum toxin into the skin is now an established mode of treatment for excessive sweating. Its advantage over other modes of treatment include less frequent side effects and long duration of action after a single injection (3–9 months) eliminating the need for taking daily oral medications or daily application of topical creams.

Over the past 15 years, several high quality studies (comparing toxin injections with placebo injections) have demonstrated that injections of BoNTs into or under the skin, reduces the volume of the local sweating way out of proportion to placebo injections. Although the injection are painful (despite topical application of numbing cream before injections), 90% of the adults tolerate the injections and prefer 15–20 min of discomfort for every 3–9 months to the debilitating excessive

sweating. At the present time only Botox is FDA approved for management of hyperhidrosis; the medical literature however indicates the other two type A toxins (Xeomin and Dysport) and the type B toxin (Myobloc) are equally effective for this indication. Long term follow ups exceeding 10 years are now available and have shown continued efficacy of BoNT injections in hyperhidrosis with no reduction of efficacy after prolonged use.

Technique of Injections

Injections are performed with a thin (guage 30) and short needle (½ inch) into the skin, using a grid like scheme (Figs. 13.3 and 13.4). Since the skin is sensitive, it is advisable to numb the skin before injections. Emla cream can be applied to the intended areas (axilla, palm, sole of the foot) an hour before the injections. The author, also uses a numbing spray intermittently during the injection that provides additional numbing of the skin for a few seconds. The injected dose of toxin per site should be very small in order to avoid weakening of the muscles underneath the skin. This is particularly important in the palm area to avoid weakness of the fingers. For Botox and Xeomin, the advocated dose per injection site is 2–2.5 units. For Dysport (another type A toxin) and Myobloc (type B toxin) the units are 2.5 to 3 times and 40–50 times larger than Botox units, respectively. Most authors inject at 20 sites in each armpit and inject more sites for the palm and foot injections. Usually fingers and toes are also covered in the plan of injections (Fig. 13.3). Excessive sweating in bilateral, hence injections should cover both sides. In experienced hands Botox (or other toxins) injections can be performed quickly over 10–15 min for

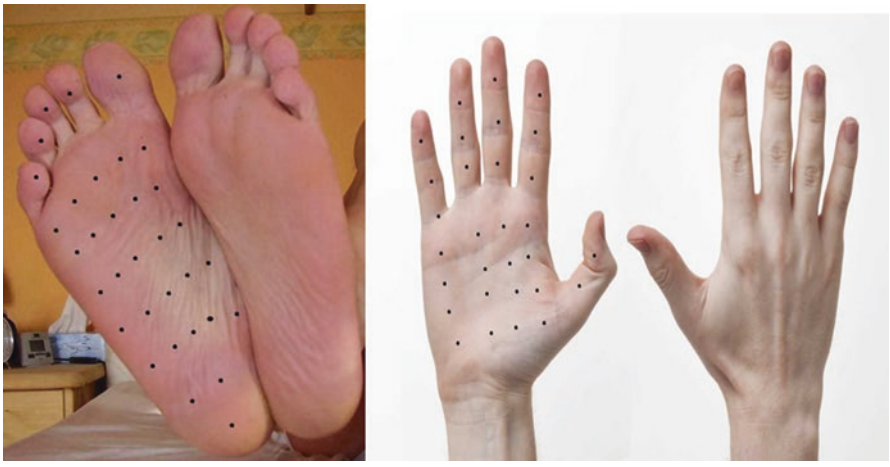

Fig. 13.3 The sites of Botox injections for excessive sweating of the sole of the foot and plam tuition. The images slightly modified from wikemedia under creative common attribution

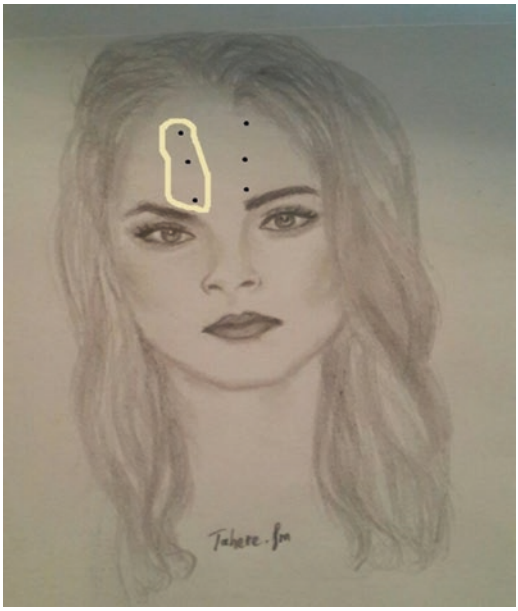

Fig. 13.4 Botox injection for recalcitrant itch of the right forehead (area of itch is painted in yellow). Injection dose is 5 units of Botox per site- Dawing courtesy of Dr.Tahere Mousavi

each side. Side effects are uncommon and usually limited to local pain and minor bleeding. As other indications of BoNT therapy, a mild, transient flu like reaction may occur in 5–10% of the patients.

Case Report

A 42 year- old women was referred to Yale Botulinum Toxin Clinic for excessive seating of the sole of the feet since childhood. Her mother and younger brother had the same problem since early teens. She had no other health problems. She has tried different anticholinergic medications for management of her foot hyperhidrosis but the effect was modest and oral drugs caused disturbing dry mouth and blurring of vision. After numbing the sole of the feet with Emla cream she was injected with Botox on both feet (Fig. 13.3). The total dose per feet was close to 100 units; 2.5 units was injected per each site. She tolerated the procedure and had no side effects. Over the next 6 years of follow up, patient visited the clinic every 4–6 months and received similar injections. She continued to do well; each time expressing satisfaction with treatment.

Current strategies for treatment of drooling (sialorrhea) and excessive sweating (hyperhidrosis) are discussed in detail in several recent publications [1–8].

Potential Indications of BoNT Therapy in some Skin Disorders: Intractable Itch and Psoriasis

Recalcitrant Ich

Itch is an irritating sensation involving a part of skin often provoking a scratch response to relieve it. In many cases, acute itch is part of a body defense mechanism against an external noxious stimulus. Chronic itch can be seen in a variety of medical diseases such as skin disorders (i.e. psoriasis), systemic disorders (kidney or liver dysfunction), infectious conditions and nerve damage from an external cause. It is believed that itching sensation is conveyed to the brain by very thin nerve fibers similar to those that carry pain sensation.

Treatment of persistent itch includes non-pharmacological approaches, pharmacological approaches an neurostimulation. Non-pharmacological approaches include wearing protective garments, avoiding warm temperature and ultravioletB exposure. Pharmacological therapy includes application of capsaicin, lidocaine 5%, cortisone creams and tacrolimus. Anecdotal reports suggest efficacy of antiepileptic drugs pregabalin, carbamazepine and lamotrigine in management of chronic itch disorder. Transient stimulation of peripheral nerves (neural stimulation) has been reported to provide temporary relief from recalcitrant itch in a limited number of patients.

After injection into the muscle or skin, botulinum toxins block the release and action of several specific proteins which are important in transmission of pain sensation to the brain. Some of these proteins such as histamine and substance P are believed to be important in the pathophysiology of itch as well. In 2008, the author's group at Yale University were first to report the utility of botulinum toxin injection into the skin in a patient with recalcitrant facial itch [9]. Four years later, another group of doctors published a similar result with botulinum toxin therapy in chronic itch disorder.

Case Report

A 55 year- old women presented to Yale Botulinum toxin clinic for evaluation of intense right facial itch for the past 6 years. The affected area extended from the medial part of the right eye brow up across the forehead ending at the hair line. She had had a right frontal sinus injury 14 years ago. The skin at the region of forehead surgery had a tingling sensation for several years before the intense itch developed in the same area. Patient complained of poor quality of life due to her debilitating facial itch. Treatment with oral medications and local novocaine injections provided minimal relief. Botox was injected into the forehead at the area of intense itch (5 units at three sites –Fig. 13.4). Similar areas were injected on the left side of the forehead in order to maintain forehead symmetry.

After a week, the patient reported marked reduction of the itch intensity which lasted for months. The patient moved out of the area and lost to follow up for

6 months. She returned to the clinic a year later for a second injection. The injection again relieved her itch. In her words "Botox injection was the only thing that helped her itch problem ".

Psoriasis

Psoriasis is a common skin lesion characterized by proliferation of skin cells causing raised and discolored skin areas. The affected skin areas often itch and cause local pain and are cosmetically unpleasant. In plaque psoriasis lesions can affect any part of the body whereas in inverse psoriasis, psoriatic lesions involve the area of skin folds (arm pit, groin, etc). Psoriasis is considered an autoimmune disease in that the immune system of the patient mistakenly attacks the patient's own tissue, skin in case of psoriasis.

In 1998, Dr. Zanchi and his colleagues published results of their study on 15 patients with inverse psoriasis who were given Botox injections into the psoriatic skin lesions [10]. Lesions were in the armpit, groin and in several women below the breast in the inframammary fold. Injections were performed in a grid-like pattern, 2.8 centimeters apart with each site receiving 2.4 units of Botox. Patients were followed for 2, 4 and 12 days. All patients reported improvement of itch and local pain. Photographs of the lesions demonstrated notable improvement of redness and healing of the lesions in 13 of 15 patients. In the following years, other investigators have published case reports demonstrating clearing of skin lesions in both plaque and inverse psoriasis after botulinum toxin injections Fig. 13.5.

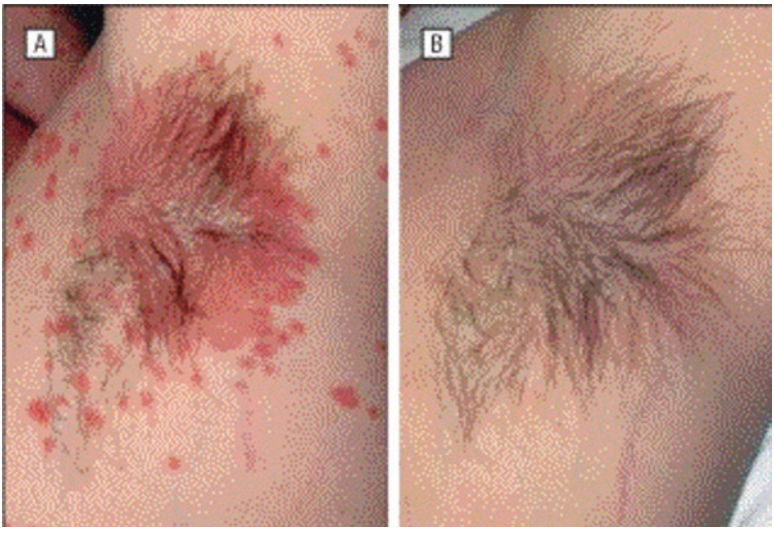

Fig. 13.5 Psoriasis of armpit: a- before and b- after treatment with Botox injections (100 units). From Saber and Co-workers Archieves of Dermatology 2011. Printed with permission from Publisher American Medical Association

Conclusion

Local injections of botulinum toxins (A or B) have been shown to be effective in reducing saliva and sweat in patients affected by drooling or excessive sweating. This mode of treatment is already practiced by many clinicians to alleviate many patients' symptoms. Botulinum toxin treatment of drooling and excessive sweating is safe; with only infrequent and minor side effects. Limited data from uncontrolled studies (no comparison with placebo) suggest that injection of Botox into the skin can alleviate local pain and itch in patients affected by psoriasis and heal their skin lesions. Case reports suggest that recalcitrant itch due to other causes may also respond to injection of Botox into the affected area.

References

1. Hosp C, Naumann MK, Henning H. Batulinum toxin treatment of autonomic disorders. Focal hyperhidrosis and sialorrhea. Semin Neurol. 2016;36:20–8.
2. Dressler D. Botulinum toxin therapy. Its use for the neurological disorders of autonomic nervous system. J Neurology. 2013;260:701–13.
3. Naumann M, Dressler D, Hallet M, et al. Evidence–based review and assessment of botulinum toxins for the treatment of secretory disorders. Toxicon. 2013;67:141–53.
4. Lakraj AA, Moghimi N, Jabbari B. Sialorrhea: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins (Basel). 2013;5:1010–31.
5. Lakraj AA, Moghimi N, Jabbari B. Hyperhidrosis: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins (Basel). 2013;5:821–40.
6. Restivo DA, Panebianco M, Casabona A, Lanza S, Marchese-Ragona R, Patti F, Masiero S, Biondi A, Quartarone A. Botulinum toxin A for Sialorrhoea associated with neurological disorders: evaluation of the relationship between effect of Treatment and the number of glands treated. Toxins (Basel). 2018 Jan 27;10(2). pii: E55.) https://doi.org/10.3390/toxins10020055.
7. Rosen R, Stewart T. Results of a 10-year follow-up study of botulinum toxin A therapy for primary axillary hyperhidrosis in Australia. Intern Med J. 2018;48:343–7.
8. Sridharan K, Sivaramakrishnan G. Pharmacological interventions for treating Sialorrhea associated with neurological disorders: a mixed treatment network meta-analysis of randomized controlled trials. Clin Neurosci. 2018;51:12–7.
9. Salardini A, Richardson D, Jabbari B. Relief of intractable pruritus after administration of botulinum toxin A (botox): a case report. Clinical Pharmacol. 2008;31:303–6.
10. Zanci M, Favot F, Bizarrini M et al. Botulinum toxin type- A for treatment of inverse psoriasis. J Eur Acad Venerol. 2008;31:303–6.

Chapter 14
Botulinum Toxin Treatment in Children

Introduction

The first childhood medical disorder that was researched and received approval from FDA (1989) for botulinum neurontoxin therapy (BoNT) was strabismus (squint, crossed eyes) – a predominantly childhood ailment (see Chap. 1- history). Approval for other potential indications in childhood lagged behind adult indications due to safety concerns. Currently, botulinum toxin therapy in children has been approved by FDA for spasticity (stiff muscles associated with cerebral palsy, stroke, brain and spinal cord trauma), involuntary movement disorders (dystonia), crossed eyes (strabismus) drooling. Other adult conditions in which botulinum toxin therapy has been approved in adult such as bladder dysfunction, drooling/excessive sweating and chronic migraine, are actively under investigation when they manifest in children.

As discussed in the first three chapters of this book, only two of seven serotypes of BoNTs (types A and B) are currently in medical use. Three type A toxins – Botox, Xeomin and Dysport, and one type B toxin (Myobloc) have FDA approval for use in the US. The units of these marketed formulations are not truly comparable, but an approximation is often used in medical research: 1unit of Botox = 1unit of Xeomin = 2.5 units of Dysport = 40–50 unit of Myobloc.

The pharmacological characteristics, modes of preparation for clinical use and other issues differentiating these toxin formulations are discussed in the first three chapters. Safety issues with BoNT therapy with particular emphasis on children are addressed in Chap. 15.

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_14

Botulinum Toxin Therapy in Childhood Spasticity

Childhood spasticity is probably the condition for which BoNT therapy is most widely used among children. Spasticity is increased muscle tone leading to muscle stiffness, decreased range of joint movements and progressive immobility. Spasticity is associated with increased reflexes. It is caused by damage to the central nervous system- that is brain or spinal cord. The most common causes of spasticity in children consist of cerebral palsy, trauma to the brain and spinal cord as well as hereditary/genetic disorders that change the brain tissue and impair brain or spinal cord function. Untreated spasticity leads to muscle contracture a condition characterized by shortened and non-functioning muscles. In the advanced cases of spasticity, the joints also become non-functional and immobile. The spastic muscles and involved joints are often painful.

Treatment of spasticity includes both physical therapy and medicinal approach. Subtle and mild spasticity can improve with physical therapy and stretch exercises alone. In moderate or severe spasticity requires more aggressive approach to improve range of motion across the joint (s) and prevent immobility. In these cases physical therapy is often combined with pharmacological therapy. Among different anti-spasticity drugs, Benzodiazepines (Valium), Baclofen and Tizanidine are most widely used medications for treatment of spasticity. Although partially effective, the side effects of these drugs often prevent dose escalation to the level that can produce the optimal desirable results. Valium can cause drowsiness, sedation, balance problems and drop in blood pressure. Nausea, confusion, muscle weakness and drowsiness are common side effects of Baclofen. Tizanidine (Zanaflex) can cause sedation, drop in blood pressure and liver toxicity. Very severe cases of spasticity, especially when involving the legs, are sometimes treated with baclofen pump. This is an involved procedure which requires implanting a small pump into the abdominal wall that drips baclofen solution directly into the spinal fluid via an inserted tube. It requires availability of an experienced surgeon and a trained and dedicated nurse for insertion of the pump and titration of the baclofen dose for continuous infusion. Incorrect titration can lead to baclofen toxicity with serious side effects (seizures, coma).

Intramuscular injection of Botulinum toxins relaxes the muscles by blocking the release of acetylcholine, a chemical which is released from nerve endings to activate the muscle. It is this function that makes BoNT injection a desirable commodity for relieving the troublesome effects of spasticity such as stiff muscles, limitation of movements across the joints as well as muscle and joint pain. Detailed description of how botulinum toxins exert this effect on the neuromuscular junction is provided in Chaps. 1 and 2 of this book. This function is shared among all four marketed botulinum toxins(Dysport, Botox, Xeomin, Myobloc) in US. FDA approved type A toxins (Botox and Dysport) for treatment of spasticity for both upper and lower limb of adults in 2010 and 2013. Currently, Dysport (one of the three type A toxins) is the only BoNT that has FDA approval in children for lower limb spasticity (2016). However, BoNTs are also used widely “off label” for older children’s upper limb spasticity based on strong supportive literature.

Cerebral Palsy (CP)

The term cerebral palsy describes a medical condition in which children, from a very young age, develop neurological problems following brain damage. In a majority of these children, the damage happens during the first two years of life when the immature brain is very sensitive to the lack of oxygen. Birth difficulties and trauma are the leading causes of cerebral palsy.

The prevalence of in 2–3 per 1000 live births worldwide[1]. Cerebral palsy has two common forms of clinical presentation. The more common of the two, is weak and stiff limbs (spasticity). In some children abnormal involuntary movements are the prominent clinical feature of CP. Cognition is impaired in a large number of children with CP, but some children may have near normal or even normal mentation. The spastic form of cerebral palsy (commonest form), leads to limitation in range of motion of the limbs across the joints and pain in the joints and muscles. Progressive shortening of the muscles may lead to immobility. Since the life expectancy of children with CP is comparable with children without CP (near normal), CP is a major cause of impaired motor function and gait in adults. Treatment of spasticity in CP requires medications as described earlier in this chapter combined with physical therapy. For most children, however, these treatments are mostly palliative with no or little observable return of motor function.

In 1993, Dr. Andrew Koman and his coworkers were the first to show that injection of Botox into the spastic muscles of children with cerebral palsy can improve and reduce muscle tone and delay the corrective surgery to more appropriate age when the child is older[2]. In this open label study (no comparison with placebo), a majority of the 27 children who were poorly responsive to conventional pharmacotherapy demonstrated improvement in motor function. Since then, several blinded and placebo– controlled studies have confirmed that spasticity of children with CP responds well to botulinum toxin injections with ultimate improvement in quality of life similar to adults [3].

Case Report

A 16 year-old girl, with diagnosis of cerebral palsy, and weakness and stiffness of all limbs was referred to Botulinum Toxin Clinic at Walter Reed Army Medical Center in Washington DC for treatment of painful and stiff muscles. She had developed problems with motor development during infancy. She had never either walked normally, or developed normal speech. At age twelve, she was wheel chair bound and weighted 160 pounds.

Neurological examination showed a pleasant Caucasian girl who smiled frequently during examination. She had little speech output. Her cognition was slightly impaired, but she was able to communicate with opening or closing her eyes and could attempt to perform simple commands. There was marked stiffness and

spasticity of all limbs with diffusely increased reflexed. Both elbows and knees were flexes. The left hand showed flexed, clinched and immobile fingers with no function. After several attempts, she could finally to take an object (pen or pencil) with the right, but was unable to hold it for long or transfer it to the left hand.

After obtaining consent from the child and her parents, Botox was injected into the flexor of the wrist and fingers into both forearms and hands. The total dose per side was 60 units. She reported loosening of her hand and forearm muscles after a week. An examination 4 weeks after Botox injection, showed marked reduction of tone in the finger and hand muscles on both side. The left hand was now open. She could move fingers in both hands at will. When given a pen and a cup, she slowly grabbed the pen with the right hand and was able to transfer it to the left hand. She then used her mostly two functional fingers of the left hand (point and middle fingers), and succeeded to drop the pen into the cup after three attempts. Both the child and her family expressed much satisfaction with her response to the Botox treatment. Repeat injections, every three to four months produced the same effect. She reported no side effects after Botox injections.

Aside from cerebral palsy, trauma to the brain or spinal cord as well as genetic and hereditary diseases also are a major cause of spasticity in children. Spasticity caused by these conditions also responds to botulinum toxin therapy.

Technical Issues

In most CP children with spasticity, due to diffuse nature of the spasticity, the injector needs to be selective and treat the most affected muscles. In this regard parents' and child's view need to be taken into consideration. Due to safety issues, the total dose per injection should not exceed the safe levels reported in the literature. Currently, for Botox, a total dose 10–15 units/kg of body weight is considered safe by most injectors. Although the units among the toxins are not truly comparable, the following formula can be used for dose comparison among the various toxin formulations: 1Botox unit= 1Xeomin unit = 2.5 Dysport unit = 40 myobloc unit, the first three being type A toxins.

BoNT injections into upper limbs of children with spasticity is still off label (not FDA approved), though used widely due to availability of the supporting literature. For lower limb, Dysport is the only FDA approved formulation based on a phase 3 study[4] (for definition of phase 1, 2,3 clinical trials see Chap. 3). The approved label recommends 30unit/kg for one leg or 60 units/kg for both legs or up to a total dose of 1000 units, whichever is lower.

Injections are usually done without generalized anesthesia, but in some children, anesthesia may be required. In the upper limb, flexor muscles of the of the arm, wrist and fingers are mostly affected. Over flexion of these muscles due to increased tone leads to flexed elbow, flexed wrist and if finger flexors are severely affected, a clinched hand with all fingers flexed (Fig. 14.1a and b) .

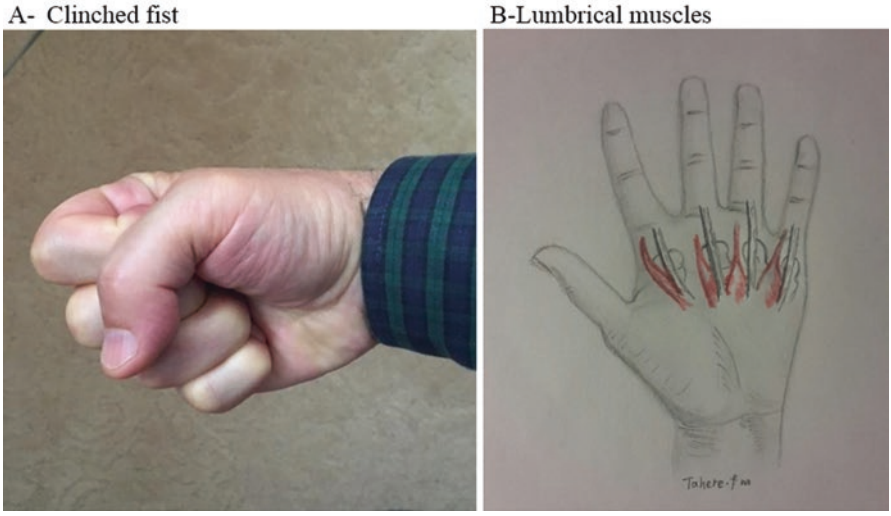

Fig. 14.1 (**a**) clinched fist position due to severe spasticity of finger flexors. (**b**) Four small lumbrical muscles of the palm contribute to spastic clinched fist by over flexing the base of the fingers over the palm. Other finger flexors in the forearm also contribute to this hand position. Drawing courtesy of Dr. Tahere Mousavi

In the lower limbs, adductors of the thigh (muscles that bring the thighs together), flexors of the knee (hamstring muscles in the back of the thigh) and flexors of the foot (gastrocnemius and soleus – Fig. 14.2b) are the most commonly affected muscles. Involvement of these two latter muscles pushes the front part of the foot down and pulls the heal up, giving the foot the appearance of a foot in a high heal shoe (equinus position- Fig. 14.2a). This is a common problem with children with CP and spasticity interfering with walking and standing.

For injections, the calf muscles are easily approached from the surface of the calf using anatomical landmarks. Ancillary techniques can be used for better localization of the muscles such as electromyography (recording electrical activity of the muscle), nerve stimulation (to identify the desired muscle by stimulating its nerve) and the ultrasound technique. Ultrasound has the advantage of directly showing the muscle and the injecting needle as well as causing no pain.

Botox, Dysport and Xeomin need to be diluted with normal saline before injection. Myobloc, a type B toxin is provided in a prepared solution forms. Botox, Dysport and Myobloc need refrigeration; Xeomin does not. Details of toxin preparation are provided in Chap. 3.

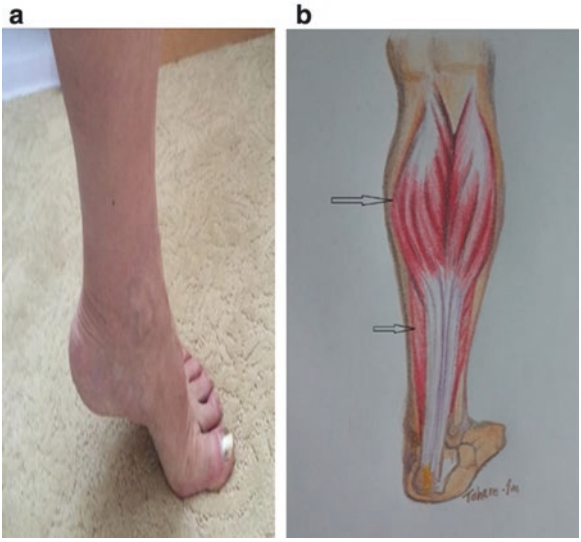

Fig. 14.2 (**a**) Equinus foot position (**b**) Gastrocnemius(*upper arrow*) and soleus (*lower arrow*) muscles of the calf that their spasticity and high tone results in Equinus foot position. Drawing courtesy of Tahere Mousavi M.D

Botulinum Toxin Therapy for Prevention of Hip Dislocation in Spasticity

In children, spasticity of the muscles around the hip joint gradually pushes the head of the long thigh bone outward from the hip joint (subluxation). In one study of 98 children with CP, continuous lateral hip migration occurred in 86% and resulted in subluxation in 11.4%[4]. In young children, hip joint subluxation is painful and can interfere with sitting and walking. Corrective surgeries are not always helpful. Botox injection into the severely spastic muscles of the thighs around the hip joints has been used to reduce the rate of hip dislocation in young children with cerebral palsy.

Treatment of Movement Disorders in Children with Botulinum Toxins

This is another major indication of BoNT therapy in childhood. Cerebral palsy and childhood diseases related to genetic or hereditary disorders can affect nerve cells deep in the brain (basal ganglia) and cause a variety of involuntary movements. Among these movements, one movement – dystonia- is particularly responsive to BoNT therapy. Dystonia is described as involuntary twisting and twitching movement of a limb or a part of it due to dysfunction of basal ganglia, a part of brain that controls and coordinates movements. Dystonic movements of the hand and finger

disrupt the performance of daily tasks and impair the child's quality of life. As drugs are often associated with side effects, injection of BoNT into the muscles involved in dystonic movements is now considered the first line of treatment for many such conditions in both adults and children.

In children, three disease conditions produce dystonia more often than others:

1. As mentioned earlier, in one type of cerebral palsy, abnormal movements are more prominent than spasticity. In children with this type of CP, dystonia of neck muscles pulls, turns and twists the neck and causes neck and shoulder pain in addition to social embarrasment. BoNT injection into shoulder and neck muscles suppresses dystonic posture and neck movements and relieves pain[5]
2. Genetic disorders in which dystonia is the main clinical feature are referred to as primary dystonias. To date, close to forty different types of primary dystonias have been described and, in more than half, the gene(s) has been identified. Although, these early onset dystonias are generalized (affecting all limbs), botulinum toxin injection can be focused on the muscles that are more severely involved (arm, leg, neck) and provide relief for the dystonia.
3. Dystonia related to chronic drug use, especially those drugs administered for treatment of depression and schizophrenia in teenagers. A group of these drugs called neuroleptics (example: haldol) are capable of producing persistent abnormal movements even after stopping the culprit drug. Hence, they are called tardive (delayed) dyskinesia (abnormal movement). Such dyskinesias (in this case also called tardive dystonia) may develop in the face, limbs or both. They may respond to injection of BoNT into the dystonic muscle. A more detail description of botulinum toxin tretmet in dystonia is given in Chap. 11.

Tic Movements

Tic is an involuntary, abnormal movement characterized by rapid onset, short duration (seconds) and repetitive nature, often preceded by an urge to move. Motor tics can be simple (just movement) or have more complex manifestations. In Tourette syndrome (named after a French physician), motor tics are associated with guttural sounds and involuntary vocalization. Repetitive, frequent motor tics involving shoulder and neck muscles are exhausting and sometimes painful. Tics have their onset in childhood. Frequent tics of Tourette's syndrome (TS) can be disabling in teenagers.

Dr. Jankovic and his group from Baylor college of medicine were first to show that shoulder and neck tics can be greatly reduced after injecting Botox into the affected muscles [6]. Botox injections also reduced the urge to move in these patients. Others have shown that injecting Botox into the vocal cord muscles (miniscule doses of 1–2 units) of children with TS can reduce vocalization (More detail of botulinum toxin therapy for tic disorders is described in Chap. 11).

Indications for Eye–Related Problems in Children

In several disease conditions, one or more muscles that move the eyes develop abnormal hyperactivity and increased tone. This hypertonic muscle (s) can interfere with normal eye movements and cause symptoms such as double vision (diplopia), blurred vision and headache. Since the chemical neurotransmitter released at the nerve endings that activate eye muscles is acetylcholine (same chemical as that of other body muscles), injection of BoNTs into the affected eye muscle can improve patients' symptoms. Before discussing BoNT therapy in children with strabismus, familiarity with basic knowledge of eye muscle- anatomy would be helpful:

Each eye has 6 muscles that control eye movements in different directions. Two of these muscles move the eyes straight up or down; they are called rectus (straight) muscles. For example, the right superior rectus muscle, moves the right eye straight up and the right inferior rectus moves the eye strait gown. There are two oblique muscles that also move the eye obliquely up or obliquely down toward the midline. There is one medial rectus muscle per eye that moves the eye straight toward the nose and one lateral rectus muscle per ach eye that moves it straight laterally (Fig. 14.3). The nerve supply for eye muscles comes from the so called cranial nerves. There are 12 nerves that after emerging from the brain provide innervation to the eyes, head and face muscles. The fourth cranial nerve innervates the oblique muscles, the sixth nerve innervates the lateral rectus muscles and the rest of the eye muscles are supplied by the third cranial nerve.

These muscles are yoked, meaning that the two muscles with opposite functions closely work with each other. For example, lateral rectus muscle of one eye and medial rectus of the other eye work together to align the axis of the two eyes in lateral and medial directions of gaze so that a single image from the two eyes is conveyed to the brain.

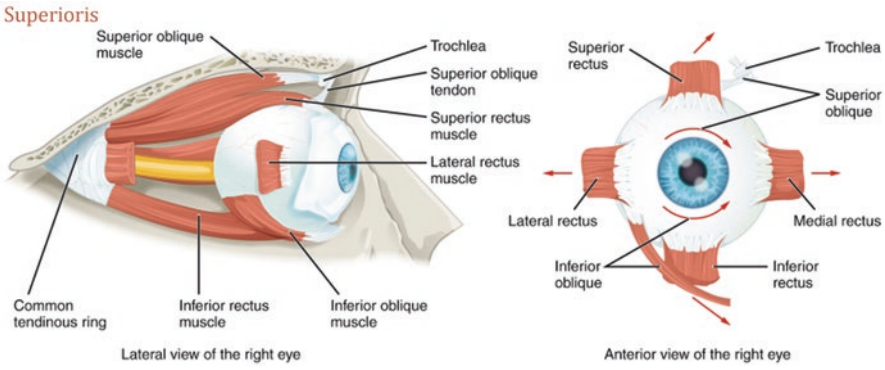

Fig. 14.3 Muscles that move the eye in different directions. From Ludwig and Czyz[7] Reproduced with permission from Stat Perls publishing 2018 and OpenStax, License CC By 3.0

A separate single and small muscle, attached to the upper lid at the midpoint above each eye, moves the upper lid up and helps to open the eyes. It is called lifter of the upper lid (levator palpebrae superioris- not shown in Fig. 14.3).

Strabismus

The word strabismus means squint in Greek**.** It results from hyperactivity of one or more eye muscles leading to impaired alignment of the two eyes**.** When the eye (s) converge abnormally (deviated medially toward the nose), strabismus it is called esotropia (crossed eyes). Exotropia, means divergent strabismus- the eye(s) are rotated outward.

Strabismus can develop in infancy, childhood or in adulthood. When it develops in infancy or early childhood (most cases), the cause is often unknown; in many older children and adults, strabismus develops after trauma to the eyes or local infections. Esotropic strabismus (crossed eyes) occurs in 1% of normally born children. In infants with strabismus, the danger is loss of vision (amblyopia) in the affected eye since brain suppresses the image that comes from that eye. The recommended management for infants with strabismus is patching one eye at a time (alternate patching) until the child grows older and can have corrective surgery or botulinum toxin injections. Surgery via cutting the fibers of the hyperactive muscle – for example- medial rectus in the case of esotropia (eye turned in) had been the main approach until late 1980s. In older children and adults, common complaints of strabismus are double vision, headaches and blurred vision.

The neurotransmitter, a chemical that is released by the nerves near the eye muscles and activate them, like that of the other body muscles, is acetylcholine. As mentioned earlier in this chapter and in more detail in Chap. 2 of this book, BoNTs block the release of acetylcholine from nerve endings. Allan Scott, an ophthalmologist in California, first introduced botulinum toxin injections for treatment of strabismus (Chap. 1, history of botulinum toxin treatment) . After decades of research on monkeys' eyes, Dr. Scott showed that injecting Botox into the hyperactive eye muscles of the patients with strabismus can relax the injected muscle, correct eye alignment and alleviate the symptoms of strabismus. In 1989, FDA approved injection of Botox into the eye muscles for treatment of strabismus. Strabismus was one of the first three FDA approvals for botulinum toxin therapy in the US - the other two were spasm of the eyelids (blepharospasm) and hemifacial spasm – both predominantly adult ailments.

Currently, it is believed that botulinum toxin therapy and surgery have comparable efficacy in correcting strabismus. BoNT therapy has three advantages over surgery:

1. Period of anesthesia is shorter
2. The local pain after botulinum toxin injection is subtle and short lived
3. The procedure is considerably shorter than surgery

The main disadvantage is the need for meticulous titration, as overdosing can lead to too much weakening of the injected muscles causing further problems such as drooping of the eyelid and persistent double vision.

Since the original observation of Dr. Scott, and his group as well as other researchers have shown the efficacy of botulinum toxin treatment in alleviating strabismus related symptoms in several studies [8, 9]. In England, Dysport, another type A botulinum toxin, is used more often than Botox for treatment of strabismus. The results of Dysport therapy for strabismus have been reported to be as effective as Botox and, in some reports even more promising. In general, esotropia (eyes turned in) responds better than exotropia (eyes turned out). In children, one injection often produces longterm effects, whereas in adults, similar to other movement disorders treated with BoNTs, repeated injections are necessary. Children younger than two years of are not usually injected since in some children, strabismus may resolve spontaneously up to that age. Recent studies are focused on longterm results of surgery compared with BoNT therapy and/ or possible benefits from combined surgery and BoNT therapy.

Technique of Injection

Currently, three methods are applied for injection of Botox or Dysport into the eye muscles for improving squint. In most cases, a short term −10 to 15 minutes- inhalation anesthesia is required. Some practitioners inject Botox or Dysport with a fine needle through the surface of the eye (conjunctiva) directly, using only anatomical guidelines. This has the drawback of sometimes missing the culprit muscle and causing spread of the toxin to unwanted eye muscles. The results can be development of double vision and drooping of eyelids. An alternative way preferred by many ophthalmologists, is starting with a small (2 mm) incision on the surface of the eye through which the muscle of choice is identified and injected . Injections are carried out with a very fine needle (guage 30). The third method is injecting the eye muscle after confirmation by electromyography (EMG). Electromyogrpahy is a procedure that records the electrical activity of the muscle. Special hollow EMG needles are available in the market that allow EMG recording as well as injection of the BoNT into the muscle via the hollow core of the same needle. The drawback is additional time spent in electromyographic identification and availability of an expert elctromyographer during the procedure.

The dose of the injected toxin (Botox or Dysport) into the eye muscles is small, only a few units (usually 2–3), compared to the much larger doses used for dystonias or spasticity.

Promoting Healing of Damaged Cornea

Trauma and infection damaging the cornea, if not managed properly, can leave a scar in the cornea leading to permanent loss of vision. Blinking and exposure to air can further irritate the damaged area and delay or prevent healing. Injection of a small amount of botulinum toxin in the muscle that moves the eyelid up and initiates the "blink" can paralyze this muscle (levator of the upper lid) and close the eye for 2–3 months. This will prevent constant eye irritation by blinking and air exposure and facilitate healing of the damaged area.

Treatment of Excessive Drooling in Cerebral Palsy

Children and adults with severe cerebral palsy may develop excessive drooling that impairs their quality of life. Injection of BoNTs (Botox, Dysport, Zeomin, Myobloc) into the glands that secrete saliva (mostly parotid and submaxillary glands) can reduce saliva production and drooling. Both glands are easily approachable from the surface. The parotid gland in located over the angle of the jaw- barely under the skin. The submaxillary gland is located under the arch of the jaw, a few centimeters medial to the jaw's angle. Many injectors use just anatomical landmarks for injection. Since the skin is sensitive, it needs to be numbed by a numbing cream or spray or both prior to injection. Injections are performed with a very thin and small needle (½ inch, 30 guage) and quickly into two sites per gland. Some injectors prefer four site injection for the parotid gland. Using ultrasound technique is a more precise way to perform injections into these glands since ultrasound shows the gland and the needle entering it and even the volume of injected material into the gland. Side effects are pain during injection, minor self-limited bleeding and, in some cases, transient swallowing problems. The latter is more of a problem with injecting the submaxillary gland since missing it can spread the toxin close to the esophagus- the tube that connects the mouth to the stomach. For submaxillary gland, injections under ultrasound are highly advisable. For a more detailed description of BoNT injections for drooling and anatomical information related to the salivary glands the reader is referred to Chap. 13 of this book. Recent literature indicate that injection of botulinum toxins into the slaivary glan of children is highly effective to reduce disabling drooling of children with cerebral palsy [10].

Conclusion

Botulinum toxin therapy can improve a variety of symptoms in children. High quality studies demonstrated efficacy of BoNT therapy in spasticity of different causes (CP, neurodegeneration, trauma), involuntary movements (dystonia, tics), squint

and crossed eyes as well as frequent drooling. The incidence of side effects is low when the procedure is performed by experts applying recommended doses. In children, however, the issue of safety is of primary concern. Rare serious side effects are reported in children when treating spasticity even with small doses of the toxin (see Chap. 15 on safety issues). Longterm studies of BoNT therapy in children with spasticity and strabismus have demonstrated sustained efficacy with repeated treatments. Cost effectiveness of BoNT therapy in spasticity compared with oral medications has been documented in several studies (see Chaps. 15 and 16 which covers cost effectiveness, insurance issues and patient support).

References

1. Colver A, Fairhurst C, Pharoah P. Cerebral palsy. Lancet. 2014;383(9924):1240–9. https://doi.org/10.1016/S0140-6736(13)61835-8.
2. Koman LA, Mooney JF 3rd, Smith B, et al. Management of cerebral palsy with botulinum–A toxin: preliminary investigation. Pediatr Orthop. 1993;13:489–95.
3. Hong BY, Chang HJ, Lee SJ, et al. Efficacy of repeated botulinum toxin type A injections for spastic equinus in children with cerebral palsy–A secondary analysis of the randomized clinical trial. Toxins (Basel). 2017 Aug 21;9(8)
4. Pascale Leone SI. Use of of botulinum toxin in the preventive and palliative treatment of the hips in children with infantile cerebral palsy. Rev Neurol. 2003;37:80–2.
5. Koukouni V, Martino D, Arabia G, Quinn NP, Bhatia KP. The entity of young onset primary cervical dystonia. Mov Disord. 2007 Apr 30;22:843–7.
6. Kwak A, Hanna PA CH, Jankovic J. Botulinum toxin in the treatment of tics. Arch Neurol. 2000;57:1190–3.
7. Ludwig and Czyz CN. Anatomy, Head, Eye muscles. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; –.2017 Dec 11; 2018 Jan. PMID:29262013.
8. Crouch ER. Use of botulinum toxin in strabismus. Curr Opin Ophthalmol. 2006;17:435–40.
9. Basar E, Arici C. Use of botulinum neurotoxin in ophthalmology. Turk J Ophthalmol. 2016;46(6):282–90.
10. Mahadevan M, Gruber M, Bilish D. Botulinum toxin injections for chronic Sialorrhoea in children are effective regardless of the degree of neurological dysfunction: a single tertiary institution experience. Int J Pediatr Otorhinolaryngol. 2016 Sep;88:142–5. https://doi.org/10.1016/j.ijporl.2016.06.031. Epub 2016 Jun 11.

Chapter 15
Why Neurotoxin Treatment is Generally Safe? What is the Long-Term Efficacy

Botulinum Neurotoxin (BoNT), produced by the bacteria- clostridium botulinum, is one of the most potent bacterial toxins known to mankind. These bacteria are present in the nature and eating food contaminated by this toxin causes a serious disease called botulism. In older days, most cases of botulism were fatal. Currently, with availability of modern intensive care units and the level of respiratory support, most patients survive if diagnosed early.

The patients' safety with BoNT therapy, has been a concern since the early days of Botox's introduction as an injectable medicinal agent by Allan Scott in 1970s (Chap. 1). Animal studies were conducted to define dangerous dose levels with Botox treatment. In monkeys with comparable body size to human, injection of 3000 units of Botox was found to be lethal. This suggested a level of safety for the early FDA approved indications of Botox therapy such as injections of small eye muscles (for correction of crossed eyes) and for involuntary facial movements (facial spasms). In these conditions, the total dose of Botox injected per session was often below 50 units since the muscles were of small size.

A new era of concern began with emerging indications of botulinum therapy for larger muscles such as neck and shoulder muscles in case of cervical dystonia (involuntary movements and postures of neck and shoulder (see Chap. 11) and when BoNTs were used for large limb muscle of the patients with spasticity. Spasticity (increased muscle tone with muscle stiffness) can occur as the result of such common neurological problems as stroke, multiple sclerosis and trauma to the brain and spinal cord (see Chaps. 6, 7). With FDA approval of BoNT therapy for cervical dystonia and spasticity, these two conditions became the most frequent indications for BoNT therapy. It soon became apparent that many patients with these two conditions, specially spasticity, require doses larger than a couple of hundred units. Allan Scott's limited observations in 1980's showing no serious side effects with Botox doses of up to 300 units (in spasticity), suggested that doses higher than 300 units may be safe in human subjects. Currently, three BoNTs, Dysport, Botox and Xeomin are approved by FDA for treatment of spasticity (see Chap. 3 for details). Dysport is the only drug that is approved for lower limb

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_15

spasticity in children. In addition to these type A toxins, FDA has approved also a type B toxin (Myobloc) for treatment of cervical dystonia. Currently, only type A and B toxins are suitable for clinical use. For description of type A and B toxin's characteristics, the reader is referred to Chaps. 2 and 3 of this book.

Since the units of BoNTs are not truly interchangeable, the safety issues with BoNTs need to be addressed in the context of the particular BoNT used. The following, is an approximation of units among toxins: 1 Botox unit = 1 Xeomin unit = 2.5 Dysport unit = 40–50 Myobloc unit. Other FDA approved indications of BoNT therapy consist of chronic migraine (Botox), bladder dysfunction (Botox), facial lines and cosmetics (Botox, Xeomin, Dysport), autonomic disorders such as excessive perspiration or salivation/drooling (Botox, Xeomin, Dysport) and strabismus/squint (Botox).

The safety issues with BoNTs are twofold;

1. The presence of small amount of human serum albumin as a component of BoNT preparation could potentially cause problems. It is known that a virus like agent -Prion that causes a very rare, but devastating neurological disorder can potentially be transmitted from human to human through injections of human serum albumin. The disease is called Creutzfeld- Jacob disease (CJ) named, after two physicians who first described it. It leads to mental deterioration, seizures and incapacity. At the end of 20th century, a variant of CJ virus caused "mad cow "- disease in England and Europe. To date, after almost 30 years of Botox therapy, the past 15 years of which has included many millions of injections worldwide, there has not been any documented case of CJ disease that could be related to Botox injections. It is therefore, generally, believed that the chance of getting CJ- disease from Botox treatment is extremely remote.
2. The side effect related to the main mechanism of action of Botox and other BoNTs namely blocking the release of acetylcholine from the nerve-muscle junction. Acetylcholine, a well- known chemical, is released at nerve endings after receiving signals from brain to activate the muscle. Through this function, BoNT injections into muscles improve and reduce involuntary movements and muscle stiffness as well as spasticity secondary to brain trauma or stroke. The effect of any type of botulinum toxin after an intramuscular injection, usually lasts for 3 to 4 months. However, if the effect of injected BoNT over nerve-muscle junction is excessive, instead of inducing a mild weakening that has a therapeutic, good effect, the muscle may lose completely its function and become paralyzed. Focal loss of muscle function for weeks or months is troublesome and, in case of paralysis of muscles involved in swallowing may require feeding through the nose and close monitoring to avoid aspiration. This is also a concern when the neck muscles are injected, especially in inappropriate sites or with inappropriately large doses. If the muscle weakness caused by BoNT injection is severe and it extends beyond the injected muscle to affect many muscles in the body, it can theoretically cause botulism. Botulism can be fatal as it can affect the breathing muscles, requiring respiratory support in the intensive care unit. Regarding these concerns, in 2009, FDA inserted a black box warning in all

botulinum toxin brochures indicating the danger of potential spread and serious complications with botulinum toxin therapy and serious complications.

Over the past 15 years, several studies have focused on assessing the safety of BoNT injections in adults and children. A summary of some high- quality studies (placebo controlled) with sizeable number of studied patients (>50) and their conclusions regarding safety are presented in the following pages.

BoNT Studies of Spasticity in Adults

Dr. Gracies and his co-workers studied 156 patients with Dysport injections into spastic muscles of the leg that had developed secondary to stroke or head trauma [1]. The patients were divided into three groups receiving either placebo or Dysport 1000 and Dysport 1500 units. Each group consisted of 52 patients. The study was double-blind (both physician and patient) and placebo controlled. It was conducted in multiple centers. The positive impact of Dysport in improving spasticity and patients' quality of life resulted in subsequent approval of Dysport by FDA for use in the US for lower limb spasticity (2017). The authors reported that side effects were slightly more in the toxin group compared to the placebo, but there were no serious side effects. Three patients developed transient swallowing difficulties and three had mild transient diffuse muscle weakness. Furthermore, in a subsequent analysis of a subgroup of this study who had paralysis in one side with spasticity due to stroke or trauma, Dr. Marciniac and her co-workers also found also no serious side effects. The most common side effect was transient inflammation of the nose and throat (pharyngitis); this side effect was found in 5.7% of the toxin groups [2].

In another study published in 2015, the authors assessed the efficacy of Dysport in three group of patients, each consisting of 81 patients who received Dysport injections of 500 and 1000 units and saline injections [3]. Patients had muscle spasticity (stiffness and increased tone) secondary to stroke or trauma. Although side effects were higher in the two toxin groups- 7% and 9% in low and high dose groups, respectively, compared to 2% observed in the placebo group- there were no serious side effects. The most common side effect in the toxin groups was mild and transient muscle weakness.

Dr. Elovic and his co-workers conducted a blinded and placebo- controlled study with Xeomin in 317 patients with adult upper limb spasticity [4]. Xeomin and saline (placebo) were injected into the muscles of 210 and 107 patients, respectively. Xeomin is another type A, FDA approved BoNT with units comparable to Botox. The following doses were used for different areas of the upper limbspasticity; flexed elbow, 200 units- flexed wrist, 150 units- clinched fist, 100 units. Authors noted significant improvement of spasticity and quality of life in patient who received Xeomin. No serious treatment -related side effect was noted in any patient. The most common side effect was dryness of the mouth which was noted in 4 patients in the Xeomin group and 1 patient in the placebo group.

In 2003, Dr. Pittock and his colleagues published a study in which intramuscular injection of Dysport was compared with placebo in 243 patients with stroke related spasticity [5]. Patients were divided into 4 groups; one group received placebo (saline) and the other three received three doses of Dysport, 500, 1000, 1500, respectively. The study was double- blind meaning neither the patient nor the injecting physician knew what was injected into the muscle. The study showed that Dysport injections reduced muscle stiffness and muscle pain as well as the use of walking aids. No serious side effects related to treatment was reported. The frequency of adverse effects was comparable between Dysport groups and the placebo group ranging from 29 to 33%. Most adverse effects were mild or not related to treatment. Two concerning adverse effects, were reported as "severe" in the Dysport group; one patient developed difficulty in swallowing and the other demonstrated deterioration of walking. The authors did not report how long these symptoms lasted.

In another study, asessing the efficacy of Botox in ankle flexor spasticity, the authors injected 200 and 300 units of Botox into the muscles that flex and invert the foot [6]. Patients had pain in calf muscles and difficulty in standing and walking. Botox injection reduced patients' pain and improved their walking. Authors noted 22 non-serious adverse effects, unrelated to treatment. There was no difference between the Botox and placebo group regarding the frequency of adverse effects.

Dr. Wein and his colleagues conducted a large multicenter study with Botox evaluating the effectiveness of this toxin formulation in reducing spasticity and pain [7]. The study had two arms; the first being blinded (comparing Botox effect with placebo) and the second phase was open label (no placebo), further assessing effectiveness of Botox over one year. The first study included 468 and the second study 407 patients. These researchers found that injection of 300 and 400 units of Botox into the leg muscles improved muscle pain and reduced abnormally high muscle tone along with significant improvement of leg function. Treatment related adverse effects were noted in 10% of the toxin group versus 7.1% of the placebo (saline) group (no statistically significant difference). None of the treatment related adverse effects were considered serious. Pain at the site of injection and nasopharyngitis were the two most common side effects but occurred with comparable frequency in the toxin and placebo groups. For Botox and Xeomin, FDA approved an upper limit of 400 units per session for treatment of upper limb spasticity (approximately 1000 units of Dysport).

The above reported low incidence of serious side effects in the BoNT (Botox, Dysport, Zeomin) injected patients conducted on large number of patients with spasticity encouraged researcher to study the safety of doses higher than 400 units for this indication. In practice, many stroke or trauma patients have severe spasticity in more than one limb and 400 units of Botox or Xeomin may not be enough to cover two or three limbs.

Dr. Dressler and his colleagues researched the safety of high doses of Xeomin (> 400 units) which was injected to 100 adult patients, half with spasticity and half with involuntary movements [8]. Xeomin is a FDA approved BoNT with units comparable to Botox. In most patients, the injected dose was between 410 to 700 units

(average 570 units). Two patients received 1000 units and 4 patients received 1200 units. Close to half of the patients reported mild side effects but, except difficulty in swallowing, none appeared to be related to BoNT treatment. This side effect was noted in 8% of the patients with cervical dystonia (involuntary neck movements). None of the patients with spasticity, even those few, that had received the highest doses of 1000 and 1200 units showed any systemic reactions or manifested any signs suggestive of botulism.

In a more recent study, Wissel and co-workers have demonstrated that escalation of Xeomin doses from 400 units to 600 and to 800 units in patients with spasticity is well tolerated and produced no serious side effects [9]. The study group consisted of 155 patients who developed limb spasticity secondary to brain damage. One upper limb was injected during the study. Treatment related adverse effects included pain in the injected limb (3 patient), mild difficulty in swallowing and diffuse muscle weakness (2 patients each). Double vision, constipation, slowing of heart rate was noted in one patient each. All adverse effects resolved in 4–6 weeks.

BoNT Studies of Spasticity in Children

Spasticity is a major handicap for small children affected by conditions that damage the brain and spinal cord during neonatal period, infancy and childhood. The leading causes of spasticity in children are cerebral palsy, and trauma to the nervous system, as well as genetic disorders that affect the brain from early childhood (see Chap. 14). As the emerging studies demonstrate that childhood spasticity may improve with escalation of the dose of injected botulinum neurotoxin, the issue of child's safety becomes a prime point of focus and concern for researchers and clinicians who work in this field. Researchers tried to establish a safe ceiling for the total dose of toxin used for treatment of spasticity. This safety ceiling is represented as units of injected toxin per/Kg of body weight. Dr. Kat Kloski's recent publication [10], discusses safety issues in childhood and includes the figure below showing the escalation figures for the maximum dose for children published by researches since 1993 (Fig. 15.1).

Table 15.1, represents the safety data described in the high quality publications (comparing toxin with placebo) regarding the use of BoNT therapy in children for the past 20 years.

The aforementioned data from well-crafted and high quality studies indicate that serious and life threatening side effects are exceedingly rare in botulinum toxin treatment of spasticity. Hence, the four US marketed BoNTs (Botox, Xeomin, Dysport, Myobloc) can be considered generally safe for treatment of spasticity in adults and children. However, since serious side effects have been reported to FDA (mostly from case observations and low- quality data), the injector needs to be alert to such rare occurrences. In rare cases, spread to remote sites may occur leading to such symptoms as difficulty in swallowing after injection of a limb muscle. In high quality studies of spasticity, however, most such cases has been mild and self-limiting.

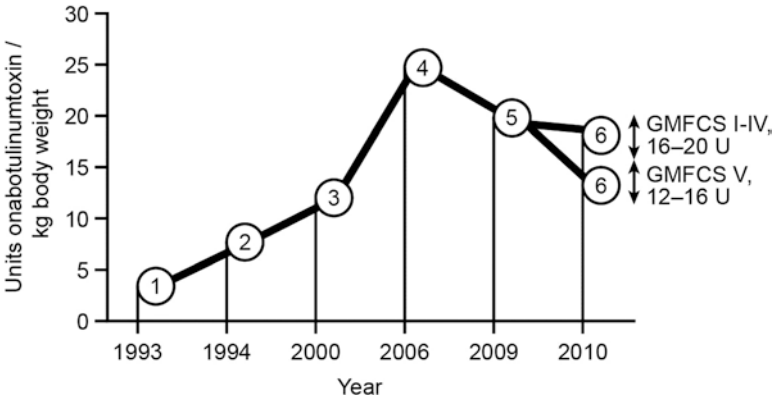

Fig. 15.1 The ceiling dose of Botox used by researchers in various publications since 1993. From Stroble and co-workers published in Toxins 2015. Reproduced with permission from publisher, MDPI

Familiarity with anatomy of the muscles, characteristics of different toxins and relative dose equivalencies among toxins is a knowledge that is essential for treatment of spasticity. In children, study of the maximum safe dose toxin dose per session is an evolving research issue. Based on current literature, most injectors believe that a maximum dose of 15–16 units per Kg of body weight per session is safe.

Botulinum Toxin Treatment of Cervical Dystonia in Adults

Cervical dystonia is mainly an adult disorder, usually presenting after age 40 years. Patients' involuntary movements (dystonia) manifest as twisting and turning of the neck and shoulder muscles. Abnormal postures of the neck such as turning or tilting to one side are common features of this disorder. After spasticity, cervical dystonia is the most common condition for which that BoNT therapy with higher doses of the toxin may be required. In case of Botox, some patients may need over 400 units injected into the affected muscles to attain the satisfactory response. In Table 15.2, the safety information regarding BoNT therapy in cervical dystonia is presented along with the type and dose of the toxin. Only information from high quality and carefully crafted studies that compared the effects of the injected toxin with placebo are listed in this table. Since formulation of some toxins (for example Botox) has improved since 1997, the Table 15.2 includes only the data of the past 20 years.

The above- mentioned studies of botulinum toxin treatment in cervical dystonia (Table 15.2) indicate that the four FDA approved toxins are generally safe for this indication. However, treatment of cervical dystonia with botulinum toxins predisposes the patient to swallowing difficulty (dysphagia); swallowing difficulty is not an uncommon side effect and is more common when higher doses of the toxin are injected. Fortunately, most such cases are mild and self-limiting. Avoiding

Table 15.1 Double blind, placebo-controlled studies with BoNTs in children with spasticity

Study – Year published	Age range	Muscles involved by spasticity	Number of children	Type of toxin	Dose per session	Safety data, adverse effects (AEs)
Delgado et al. 2016	2–17 years	Calf muscles foot	241, 226 completed study	Dysport	10 and 15 units/kg	The treatment related AEs were all mild and transient and more in the placebo group (fever, weakness, fatigue, walking problem, incontinence – Each one case in toxin group No serious side effects.
Copeland et al. 2014	2.3–16 years	Calf and thigh muscles	41	Botox	12 units/kg not exceeding 400 units	Few patients reported as having serious side effects (nausea, vomiting, diarrhea, seizure) but not clear if toxin was the culprit. Same incidence in the placebo group
Koman et al. 2013	3–18 years	Upper limb muscles	73	Botox	Ranged between 1.4 to 12.5 units / kg	Adverse events were considered mild to moderate and statistically not different from the placebo group (29 reported in placebo and 25 in the Botox group).
Moore et al. 2008	2–8 year	Leg muscles	40	Dysport	30 units/kg	Adverse effects were mild and noted in both Dysport and placebo groups with similar frequency. No serious side effects were noted.
Bjorsen et al. 2013	Mean age: 5.4 years	Calf muscle	33	Botox	12 units/kg	Mild transient side effects – No difference between Botox (n = 30) and placebo(n = 26). Three children required ibuprofen for pain at injected site

(continued)

Table 15.1 (continued)

Study – Year published	Age range	Muscles involved by spasticity	Number of children	Type of toxin	Dose per session	Safety data, adverse effects (AEs)
Kawamura et al. 2007	Mean age: 6.2 years	Upper limb	39	Botox	Two groups 10 and 20 units/ kg	Considered mild: Week grasp, 3 in low dose and 2 in high dose groups. Fatigue 2 low dose 1 high dose. All fully recovered.
Mall et al. 2006	Mean age: 6 years	Thigh muscles	61	Dysport	30 units/ kg- maximum 1500 units/ session	Recorded as mild to moderate. Most frequent AE's were difficulty in swallowing, weakness and urinary incontinence. They were transient and slightly more frequent in the Dysport group.
Baker et al. 2002	Mean age: 5.2 years	Calf muscles	125	Dysport	10,20 & 30 units/kg	Falls (7), pain (8) and asthenia (4) were most common adverse effects with Dysport- most side effects were mild. No serious TRAE.
Ubhi et al. 2000	2–16 years	Leg muscles	40	Dysport	Two groups: 15 and 20 units/kg	Six adverse effects in the Dysport group (2 increased falls, post-injection calf pain; AEs were all mild and self- limiting.
Wissel et al. 1999	Mean age 10 years	Leg muscles	33	Botox	200	Treatment related side effects noted in 8 children- all considered mild, lasting 3–35 days, including unwillingness to walk (5), mild weakness (3), muscle soreness (2), local hematoma (1).

Table 15.2 Safety data and adverse effects of FDA approved BoNTs (Botox, Xeomin, Dysport and Myobloc) from high quality studies (placebo controlled, blinded) in cervical dystonia (past 20 years)

Authors and year published	Number of patients	Type of toxin	Dose (units)	Safety data and adverse effects (AEs)
Poewe et al. 2016	369	Dysport	500 (standard), 500 (liquid formulation)	No serious treatment-related AE (TRAE). Most common AEs were dysphagia and nasopharyngitis. Dysphagia was seen in 3.1% of patients who received the solution form and 7.1% of those who received the standard form. AEs were of mild and moderate severity
Yun et al. 2015	102	Botox	100	Neck weakness and dysphagia (8 in each toxin group); both mild and tolerable
		Dysport	250	
Evidente et al. 2013	219	Xeomin	Two groups	No serious treatment-related AEs. Incidence: 29% in 120u group and 38% in 240u group. Most AEs were mild to moderate. Dysphagia: 1–5% of the120 unit and 4–15% of the 240 unit group, respectively. No patient withdrew from the study.
			120	
			240	
Charles et al. 2012	214	Botox	360	AEs were reported in 59% of the Botox and 58% of the placebo group. Dysphagia was almost twice more common in Botox group compared to the placebo, rhinitis considerably higher in the botox group compared to placebo group. No serious adverse effects.
Comella et al. 2011	233	Xeomin	Two groups	No serious treatment-related AEs. Most SEs were mild to moderate.
			120	
			240	Dysphagia: 20% in 120 U, 16% in 240 U, 9% in placebo groups, respectively. Neck pain, dizziness, weakness, injection site pain considered severe AEs
Troung et al. 2010	216	Dysport	500	No treatment- related serious side effects. Dysphagia was the main AE noted in 5 of 55 patients (9%) in Dysport group, but none in placebo group. All AEs including dysphagia were of mild or moderate severity.
Pappert et al. 2007	111	Botox 55 pts	100	No serious treatment- related side effect. TRSE: 29% Botox. 51% Myobloc. Dysphagia, local pain, dry mouth. Dysphagia: Botox 14%, Myobloc18% (one case moderate intensity but did not require special care).
		Myobloc 56 pts	10,000	

(continued)

Table 15.2 (continued)

Authors and year published	Number of patients	Type of toxin	Dose (units)	Safety data and adverse effects (AEs)
Comella et al. 2005	140	Botox: 74 pts	250	No serious TRAE. Dysphagia: Botox 19%, Myobloc 48%
		Myobloc: 65 pts	10,000	Dry mouth: Botox 41%, Myo bloc 80% - all mild to moderate
Troung et al. 2005	80	Dysport	500	AE: Dysport 92%, placebo 79%
				Severe AEs: Dysphagia 16%, placebo 12%. No statistical difference. One patient in Dysport group had severe dysphagia
Wissel et al. 2001	68	Dysport	500	No serious TRAEs.
				Dysphagia:Dysport 3, placebo 1
				Dry mouth:Dysport 5, placebo2 neck weakness:
				Dysport 4, Placebo 0
Brashear et al. 1999	109	Myobloc	Two groups	Dysphagia: One in placebo group, 4 and 8 in low dose and high dose Dysport groups, respectively. None were severe.
			5000	
			10,000	
Lew et al. 1997	122	Myobloc	Three groups	Dyphagia: 0, 5, 3, 8 in placebo, low, medium and high dose groups, respectively (all mild).
			2500	
			5000	Dry mouth: 1,1,3,0, and pain (injection site) 2,6,10,10, respectively.
			10,000	
Brin et al. 1997	77	Myobloc	10,000	No serious TRAEs.
				Dysphagia: Toxin group: 11(6 moderate, 5 mild),
				Placebo group: 2
				Duration of moderate dysphagia:1–33 days

injection of large doses in the anterior neck muscles, knowledge of the injector of anatomy of neck muscles, and proper identification of the targeted muscle helps to avoid and minimize the potential development of this adverse effect. Employing electromyography (demonstrating the sound of muscle upon activation) or ultrasound technique (which visualizes the muscle) during the injection session also reduces the risk of experiencing dysphagia.

Long–Term Effects of Botulinum Toxins

The long-term effects of botulinum toxins have been the subject of several investigations shortly after introduction of botulinum toxin therapy to clinical medicine (1989). Investigators and clinicians were interested to know the answer to several questions:

1. Can the satisfactory response to the toxin be sustained after months and years of repeated treatment?

2. Is long-term therapy safe? Are there any unforeseen deleterious side effects that may develop with the long-term use?

In recent years, several studies have addressed the first question. Dr. Jankovic's group from Baylor College of Medicine looked at the long-term effects of botulinum toxin therapy on 111 patients with different dystonias [11] (a form movement disorder- see Chap. 11). Some patients were followed up to 20 years. They showed that patients' global response to injections improved after the last Botox injection compared to the first (3.57 over 3.18) and the mean duration of response after injection increased from the initial response of 16.33 weeks to 19.42 weeks with prolonged usage. In a large, multicenter study that included 1036 patients, researchers followed patients with cervical dystonia after repeated injections over a period of 3 years [12]. At the end of 3 years, 82.6% of the patients expressed satisfaction around the peak of the injected toxin's effect compared to slightly over half, at the beginning of therapy. In a Canadian study, Dr. Jog and his co-workers looked at the changes in quality of life in 1062 patients that had repeated Botox injections (for different indications) up to 22 years. The authors found that repeated Botox injections maintained initial improvement of quality of life over the long follow- up periods [13].

Regarding the long- term safety of botulinum toxin injections, the available data provides encouraging results. Dr. Santamato and his colleagues studied safety issues and adverse effects of high dose (up to 840 units) injections over two years in 20 patients who had developed limb spasticity after stroke. After 8 sets of injections, at two year follow-up point, no concerning safety issues were noted; specifically, there were no signs of significant spread or generalization [14]. Dr. Kenelly and collaborators [15] demonstrated that repeated injections of Botox into bladder wall maintained its efficacy over 4 years without development of any concerning safety issues (for bladder treatment with BoNTs see Chap. 8). Dr. Abaneh and his co-workers followed 32 patients with involuntary movements (blepharospasm and hemifacial spasm – see Chap. 11 of this book) for 14–17 years with repeated injections [16]. Although the mean injected dose of Botox was higher in the last year compared to the first injection, no safety issues were noted following the last set of injections. It has been shown by other researchers that in migraine, efficacy of Botox injections clearly improves after the second injection and no serious safety issues were noted in longterm treatment of chronic migraine (see Chap. 4 of this book on- migraine).

Conclusion

Botulinum toxin injected into the muscle has a potential to spread to remote muscles from the site of injection and cause serious side effects. The data from carefully crafted and placebo- controlled studies, however, indicate that the possibility of serious side effects from such toxin spread is remote and BoNT therapy is generally

safe. The efficacy of the injected botulinum toxin is maintained over years of follow-up; for some indications such as migraine, it clearly improves after repeated injections.

References

1. Gracies J-M, Esquenazi A. Allison Brashear and others. Efficacy and safety of abobotulinumtoxinA in spastic lower limb Randomized trial and extension. Neurology. 2017;89:2245–53.
2. Marciniak C, McAllister P, Walker H, other co-workers. Efficacy and safety of AbobotulinumtoxinA (Dysport) for the treatment of hemiparesis in adults with upper limb spasticity previously treated with botulinum toxin: sub-analysis from a phase 3 randomized controlled trial. PM&R. 2017;9:1181–90.
3. Gracies JM, Brashear A, Jech R, co-workers. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomized controlled trial. Lancet Neurol. 2015;14:992–1001.
4. Elovic EP, Munin MC, Kaňovský P, co-workers. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke. spasticity. Muscle Nerve. 2016;53:415–21.
5. Pittock SJ, Moore AP, Hardiman O, co-workers. A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke. Cerebrovasc Dis. 2003;15:289–300.
6. Dunne JW, Gracies JM, Hayes M, co-workers. A prospective, multicentre, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat plantarflexor/invertor overactivity after stroke. Clin Rehabil. 2012;26:787–97.
7. Wein T, Esquenazi A, Jost WH and colleagues. OnabotulinumtoxinA for the Treatment of Poststroke Distal Lower Limb Spasticity: A Randomized Trial. PM R. 2018 Jan 9. pii: S1934–1482(17)30072–2. doi: https://doi.org/10.1016/j.pmrj.2017.12.006. [Epub ahead of print].
8. Dressler D, Saberi FA, Kollewe K, Schrader C. Safety aspects of incobotulinumtoxinA high-dose therapy. J Neural Transm (Vienna). 2015;122(2):327–33.
9. Wissel J, Bensmail D, Ferreira JJ, et al. Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity: the TOWER study. Neurology. 2017;88:1321–8.
10. Kolaski K, Coman A. Botulinum toxin for treatment of spasticity in cerebral palsy. In: Botulinum toxin treatment in clinical medicine – A disease oriented approach (Jabbari B, Editor): Springer Publishing; 2018. p. 81–108.
11. Ramirez-Castaneda J, Jankovic J. Long-term efficacy, safety, and side effect profile of botulinum toxin in dystonia: a 20-year follow-up. Toxicon. 2014;90:344–8.
12. Misra VP, Colosimo C, Charles D. INTEREST IN CD2, a global patient-centred study of long-term cervical dystonia treatment with botulinum toxin. Neurol. 2018;265:402–9.
13. Jog M, Wein T, Bhogal M. Real-world, long-term quality of life following therapeutic OnabotulinumtoxinA treatment. Can J Neurol Sci. 2016;43:687–96.
14. Santamato A, Panza F, Intiso D, et al. Long-term safety of repeated high doses of incobotulinumtoxinA injections for the treatment of upper and lower limb spasticity after stroke. Neurol Sci. 2017;378:182–6.
15. Kennelly M, Dmochowski R, Schulte-Baukloh H, et al. Efficacy and safety of onabotulinumtoxinA therapy are sustained over 4 years of treatment in patients with neurogenic detrusor overactivity: final results of a long-term extension study. Neurourol Urodyn. 2017;36:368–375.24.
16. Ababneh OH, Cetinkaya A, Kulwin DR. Long-term efficacy and safety of botulinum toxin a injections to treat blepharospasm and hemifacial spasm. Clin Exp Ophthalmol. 2014;42:254–61.

Chapter 16
Cost and Insurance Issues in Botulinum Toxin Therapy

Introduction

All pharmaceutical companies that produce FDA approved Botulinum toxin products is the US have established patient assistance programs. Through these programs, help is offered to needy patients with their- out of pocket- payments. The four FDA approved botulinum toxins in the US are distributed under the trade names of Botox (Allergan Inc), Xeomin (Merz Pharmaceutical), Dysport (Ipsen) and Myobloc.(Solstice Neuroscience). The propriety names given to these toxins by FDA is onabotulinum toxin A, incobotulinumtoxinA, aboboyulinumtoxinA and rimabotulinumtoxinB, respectively. The first three, are a type A and the fourth one is a type B Toxin. Of seven distinctly defined types of botulinum toxins in nature, only types A and B can be used clinically. The reader is referred to Chaps. 2 and 3 of this book for further definition of these toxins including their molecular structure, physical properties and mechanisms of action. There are two other well known toxins (both type A) with trade names of Prosigne (Lanzhou Institute-China) and Meditox (Korea) that are widely used in Asia, but are not approved by FDA for use in the US.

For enrollment into botulinum toxin patient assistant programs, patients have to meet certain eligibility criteria. These eligibility criteria are more or less the same for all companies that produce the FDA approved toxins. The eligibility criteria consist of:

1. Age 18 years or older
2. Medical condition must be FDA approved for botulinum toxin therapy.
3. The Patient should have either no insurance or a private insurance coverage.
4. The patient should not be enrolled in a federally insured program such as Medicare, Medicaid or Tricare

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_16

The total amount of medical aid ranges from $4000 (for Xeomin and Dysport and Botox) to $5000 per year. The limit for each treatment is up to $500 per session and it can be repeated several times per year as repeat injection sessions are indicated. The aid covers both cost of the vials and payment to doctor's office for medical assessment and botulinum toxin injection. It may cover the cost of ancillary diagnostic techniques such as ultrasound that visualizes the targeted muscle (for instance in spasticity), or electromyography that locates muscle activity by recording the electrical activity of the muscle or the nerve stimulation that identifies the muscle to be targeted for injecting by moving it.

In case of patients who have insurance, the patient informs the physician's office regarding being enrolled in the patient- assisted program. The physician's office then submits a bill to the insurance company for patient assessment and procedure cost. If the patient receives an invoice asking payment for part of the bill not covered by patient's insurance, he/she can submit a copy of that bill to the patient assisted program that is geared to cover up to $500 of the unpaid bill for each treatment.

The cost of botulinum toxins varies among the states. In 2005 the price was higher in the northern states compared to western states in pharmacies and hospitals provided the toxin by the whole sale organizations. The current whole sale acquisition cost (WAC) for the three widely used botulinum toxins in US are as follows:

Botox, 100 unit vial: $ 601
Xeomin, 100 unit vial: $ 482
Dysport, 300 unit vial: $ 491

The price for 50 and 200 unit vials of Xeomin is $253 and $964, respectively. Although the units of the toxins are not truly interchangeable, each one unit of Botox approximates one unit of Xeomin and 2.5 units of Dysport.

Various strategies are used by physicians to lower the price of toxin used per patient. Some of these practices are inappropriate such as an injection arrangement called "Botox parties." Usually, practiced for cosmetic purposes that require fewer units of Botox than that used for spasticity or dystonia; a physician injects a large number of patients (20 or more) in a rapid sequence. Although somewhat cheaper for the patient, such a practice is not sound and safe since rushed injections may jeopardize the accuracy of the procedure and could potentially interrupt maintenance of full sterility.

Patients and Insurance Companies

Insurance companies use a list of different diagnoses with designated diagnostic codes that illustrate indications that a particular company has approved for botulinum toxin therapy. This list varies somewhat among different companies. In consultations with experts in the field, the companies often update this list annually or biannually. Although the list(s) are somewhat rigid, there is often some room for negotiation. In each region of the country, insurance companies have physicians in

their payroll who deal with insurance issues with medical providers. If your insurance company refuses to approve you for botulinum toxin treatment of your condition, you should ask your physician if he can call the insurance company and argue your case for you. Sometimes, a very informed nurse can do as well as the treating physician but usually the process works better when the issue is discussed by the treating and company physician. The medical conditions considered for insurance approval do not always have to be FDA approved indications. For several non-approved clinical conditions, there is now ample literature to support effectiveness of botulinum toxin therapy. Some of these off-label conditions include injection of Botox and other neurotoxins into the skin for alleviating the pain associated with shingles (post-herpetic neuralgia) or the pain in the distal part of the limbs resulting from nerve damage from diabetes or local trauma. Your treating physician can provide the company's physician, before their telephonic communication, the relevant literature that strongly supports the use of botulinum toxin injection for your medical condition. In busy practices, many physicians may not find the time to do this but I know, from personal experience, that treating physicians' calls to insurance company's physician, often succeeds in gaining treatment approval for patients.

One of the reasons for disapproval for some disorders is an insurance company policy that requires evidence for failure of other medications before botulinum toxin therapy. A brief request for approval submitted to the insurance company by the clinic staff may not provide convincing information on this issue. Again, a call from treating physician is helpful. In many instances, specific medications asked by insurance companies to be used before botulinum toxin therapy may not be compatible with the patient's age or it may interfere with other medications essential for patient's health. It is the treating physician who can best discuss and document these issues or, even better, explain it over the phone.

Contact Information for Patient Support and Co–Pay Programs in US

Dysport (Ipsen Inc): Ipsen Care Program

Telephone: 1–866–435-5677- 8 am to 8 pm. Website: Ipsencares.com

Botox (Allergan Inc): Reimbursement Solutions Patient Assistance Programs

The programs assist uninsured and underinsured patients with their treatment through the donation of Botox.

https://www.botoxone.com/ Down load program application instructions. Out of pocket costs of patients' for treatment of cervical dystonia may be covered through National Organization of Rare Diseases (NORD-rarediseases.org).

Telephone: 1–855–864-4024. Website: Cervicaldystonia@rarediseases.org

Xeomin (Merz Pharma): Xeomin Patient Co–Pay Program

Telephone: 1–888–493-6646- 8 am to 8 pm ET. Website: Xeomin.com

Myobloc (Solstice Neuroscience): Myobloc Co-Pay Program

Telephone: 1–888–461-2255- 8 am to 8 pm ET.
Website: www.myobloc-reimbursement.com

Cost Effectiveness

Botulinum toxin therapy is an expensive commodity. Depending on the indications the effect of botulinum toxin injection into the muscle lasts 3 to 9 months. The need for repeat injections to maintain long-term efficacy adds to long-term expense of botulinum toxin therapy over time. Table 16.1 shows current FDA approved indications for each of the four FDA approved botulinum toxins currently used in the US.

The high cost of botulinum toxin therapy is balanced by its long-term effect that reduces the need for daily medications. Furthermore, it has been shown that utilization of botulinum toxin therapy for its numerous indications (chronic migraine, spasticity, bladder dysfunction) clearly reduces emergency room visits and the frequency of hospitalizations. For this reason, investigators began to assess the cost efficacy of botulinum toxin therapy compared with other modes of treatment. They also studied the cost effectiveness of botulinum toxin therapy, comparing some of the four FDA approved toxins with each other. The cost efficacy studies have been published for both adult and childhood indications of botulinum toxin therapy. The results of some of these studies are presented below.

Dr. Visco and his colleagues compared the cost of Botox treatment with standard oral medications (anticholinergics) in 231 women with bladder dysfunction. Botox injection of the bladder (see Chap. 8) was as effective as the use of oral medications. The cost for Botox treatment was cheaper after six months of treatment, averaging $207/month versus $305/month for oral medications [1]. These findings were supported by a subsequent British study of 101 patients with bladder problems, in whom the cost savings in favor of Botox treatment was found to be 617 pounds per patients per year [2].

Table 16.1 Clinical indications approved by FDA for 4 types of botulinum toxin FDA approved for use in the US

Trade name	Abbreviation or Type	Manufacturer	Approved indication (FDA)	Year of FDA approval
Botox	onaBoNT-A	Allergan -Inc	Blepharospasm	1989
			Hemifacial spasm	1989
			Strabismus	1989
			Cervical dystonia	2000
			Excessive armpit sweating	2004
			Migraine	2010
			Upper limb spasticity	2010
			Lower limb spasticity (adult)	2014
			Bladder (NDO)*	2011
			Bladder (OAB)**	2013
			Forehead wrinkles	2017
Xeomin	oncoBoNT-A	Merz Pharma	Cervical dystonia	2010
			Blepharospasm	2010
			Frown lines (aesthetics)	2011
			Upper limb spasticity	2015
			Sialorrhea	2018
Dysport	AboBoNT-A	Ipsen -Limited	Cervical dystonia	2009
			Upper limb spasticity (adult)	2015
			Lower limb spasticity (children)	2016
			Lower Limb Spasticity (adult)	2017
			Wrinkles	2009
Myobloc, Neurobloc in Europe	rimaBoNT-B	Solstice, Neuroscience	Cervical dystonia	2009

*NDO: Neurogenic detrusor over-activity
**OAB: Overactive bladder (See Chap. 8)

Dr. Squenazi, a knowledgeable and well published physiatrist, in a relatively recent publication [3], discusses why intramuscular botulinum toxin injections, in the long-term, are more cost effective for patients suffering from stroke, spinal cord injury and multiple sclerosis. Such patients are affected by spasticity, a condition of heightened muscle tone and stiffness and jerkiness of the limbs, that limits their daily activities and impairs their quality of life. Botulinum toxin injection into the muscle reduces the muscle tone and improves spasticity. This allows patients to reduce, and in many instances, stop anti-spasticity medications which in many cases are poorly tolerated by elderly patients. Furthermore, relief from spasticity reduces associated muscle pain, and in some patients prevents falls resulting from poor

balance due to stiff and jerky legs. Hip fractures are costly and often incapacitating in elderly patients. A very recent review (2018), found 18 articles in the literature that specifically studied cost effectiveness of botulinum toxin therapy for treatment of spasticity in children with cerebral palsy. The review concluded that Botulinum toxin therapy was cost effective in these children but suggested studies with longer follow ups are required to see if the savings persist over years.

In a study of a large cohort of patients from US based hospitals, Dr.Hepp and coworkers found positive gains in patients with chronic migraine after Botox treatment [4]. The Botox treated group had significantly lower visits to emergency room at 6, 9 and 12 months; the visits were 21%, 10% and 20% less, respectively. The figures for reduced hospitalizations over those three time lines were 47%, 48% and 56%, respectively.

Few studies have compared two or more toxins for cost effectiveness. Drs Kazerooni and Broadhead compared cost effectiveness of Botox, Dysport and Xeomin in Cervical dystonia [5]. Cervical dystonia is a late onset movement disorder characterized by posturing and twisting of the neck as well as neck pain. It responds very well to Botox or other toxin injection into the neck and shoulder muscles (see Chap. 11 of this book). Kazerooni and Broadhead found Xeomin to be the most cost effective of the three toxins followed by Dysport. In another study of patients with dystonias (blepharospasm and cervical dystonia- see Chap. 11), Dysport was associated with the lowest possible waste (2.2%) compared to10% waste for Xeomin and 22.9% waste for Botox [6]. Drs Tilden and Guanierie also found Xeomin superior to Botox in terms of cost effectiveness when they studied patients in the Australian Health System [7]. In a recently (2018) published article, Swedish authors compared the cost effectiveness of Dysport with Botox in 159 children with cerebral palsy and spasticity; the 159 children had received a total of 341 injections. Both botulinum toxins were equally effective for this indication, but Dysport was 41% cheaper than Botox. Further studies are necessary to substantiate the results of these preliminary data.

Conclusion

Cost issues are important to the patients who receive expensive botulinum toxin therapy for management of their symptom(s). Patient co-pay programs are available through manufacturers of botulinum toxins to defray some of patients' out of pocket costs. There is evidence from published literature that despite the apparent high cost, botulinum toxin therapy is cost effective compared to other modes of therapy in management of chronic migraine, spasticity associated with stroke, multiple sclerosis, spinal cord injury and chronic bladder disorders. A limited published literature from comparative studies suggests that Botox is the least cost effective compared to Dysport and Xeomin when used for the same indications.

References

1. Visco AG, Zyczynski H, Brubaker L. Cost-effectiveness analysis of anticholinergics versus Botox for urgency urinary incontinence: results from the anticholinergic versus Botox comparison randomized trial. Female Pelvic Med Reconstr Surg. 2016 Sep-Oct;22(5):311–6.
2. Kalsi V, Popat RB, Apostolidis A, et al. Cost-consequence analysis evaluating the use of botulinum neurotoxin-a in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre. Eur Urol. 2006;49(3):519–27.
3. Esquenazi. Improvement in health care and cost benefits associated with botulinum toxin treatment of spasticity and muscle overactivity. Euro J. Neurol. 2006.;Dec;13(Suppl 4):27–34.
4. Hepp Z, Rosen NL, Gillard PG. Comparative effectiveness of onabotulinumtoxinA versus oral migraine prophylactic medications on headache-related resource utilization in the management of chronic migraine: retrospective analysis of a US-based insurance claims database. Cephalalgia. 2016;36(9):862–74.
5. Kazerooni R, Broadhead C. Cost-utility analysis of botulinum toxin type a products for the treatment of cervical dystonia. Am J Health Syst Pharm. 2015;72(4):301–7.
6. Tilden D, Guanierie C. Value health. Cost-effectiveness of Incobotulinumtoxin-a with flexible treatment intervals compared to Onabotulinumtoxin-a in the management of Blepharospasm and cervical. Dystonia. 2016 Mar-Apr;19(2):145–52.
7. Tedroff K, Befrits G, Tedroff CJ, et al. To switch from Botox to Dysport in children with CP, a real world, dose conversion, cost-effectiveness study. Eur J Paediatr Neurol. 2018;22(3):412–8.

Chapter 17
Botulinum Toxin Therapy-Future Perspectives

Introduction

In the preceding chapters, we have discussed clinical conditions in which high quality studies have demonstrated the efficacy of botulinum neurotoxins (BoNTs) in improving the symptoms of various disorders. There are many other important clinical conditions in which the preliminary results of BoNT therapy are encouraging, albeit proof of efficacy awaits arrival of positive results from well- designed and high quality clinical trials. These potential indications pertain to common medical disorders for which current medical management often provides unsatisfactory results. The challenged clinicians therefore, would welcome an alternative treatment which does not require daily use of medications while producing less side effects.

The list of potential indications for BoNT therapy is long. For this chapter we have selected potential indications in four fields of medicine. In psychiatry, we will address treatment of depression. In cardiology, treatment of irregular heart beats caused by atrial fibrillation will be discussed. In pain medicine, the use of BoNT therapy in treatment of cancer related pain, prevention of pain after surgery, temporomandibular pain and painful jaw clinching will be discussed. Finally, in dermatology, we present data that suggests efficacy of botulinum toxin therapy in relief of persistent itch and healing of chronic psoriasis.

Psychiatry – Depression

Severe depression, a major Depressive disorder (MDD), is a common disease that affects 5–10% of men and 10–25% of women [1]. Lack of interest and depressive mood of the patients leads to their functional disability. Three high quality, blinded studies have demonstrated that injection of Botox into one of glabellar muscles of

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6_17

the forehead can significantly improve depression. Glabella, is the skin above the nose and between the two eyebrows. It covers a single muscle (procerus) located at midline between the two eyebrows and the two muscles (corrugator)- one on each side above the most medial part (closest to the nose) of the eyebrows (Fig. 17.1). These muscles are also called frown line muscles as their contraction leads to frowning and pulls the eyebrows together.

Three high quality, double blind (patient and rating doctor both unaware of injected material), placebo controlled studies have shown that injection of Botox into the glabellar muscles can improve depression significantly (Table 17.1) [2–4]. Wollmer and co-workers [2], have injected Botox or placebo (saline) into the glabellar muscles of 30 patients with severe depression (15 Botox, 15 placebo). Six weeks after a single injection, the scores of Hamilton Depression Rating Scale (HDRS) were reduced by an average of 41.7% in the Botox group versus 9.2% in the placebo group ($P < 0.001$). Furthermore, considerably more patients in the Botox group expressed satisfaction with treatment. In another study of depressed patients, Finizi and Rosenthal [3] have found reduction of depression scores (using Montgomery-Asberg Depression Rating Scale) in 52% of those who received Botox into the glabellar muscles versus 15% reduction of the scores in the placebo group. In another placebo-controlled study [4] using HDRS for comparison between Botox and placebo, authors have found that 55% of those who received Botox into glabellar muscles experienced improvement of depression versus none in the placebo group.

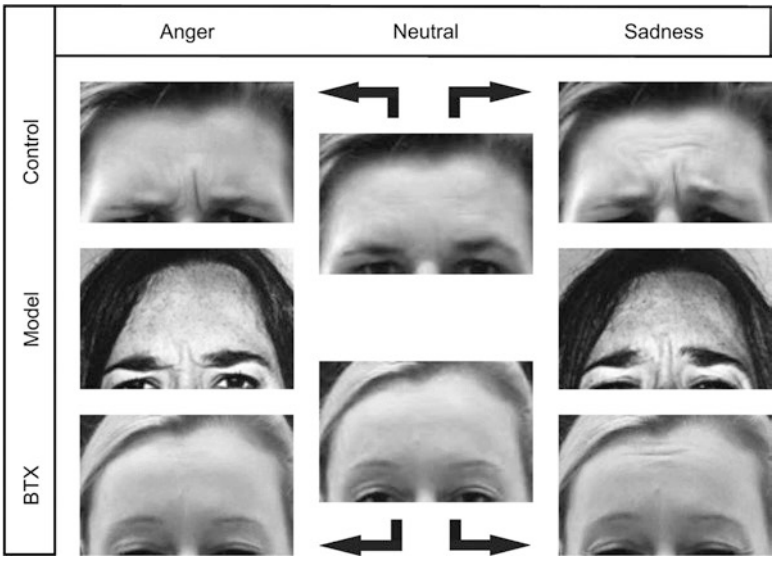

Fig. 17.1 The function of glabellar muscles-frowning during volition (not shown) and during anger and sadness. Lower part of the figure shows the effect of Botox treatment. From Hennenlotter and co-workers 2009- Journal Cerebral Cortex with permission from Oxford Academic Press

Table 17.1 High quality, blinded studies conducted on Botox effect on depression

Study	Design	N	F/M	Primary	Response and Remission rates
Wolmer et al., 2012 [2]	Double blind parallel	30	28/2	Hamilton depression rating scale-21 (HDRS-21) at week 6	Response rate: Botox 60% versus placebo 13% (p = 0.02)
					Remission rate: Botox 33% versus placebo 13%
Finzi and Rosenthal 2014 [3]	Double blind, parallel	74	69/5	50% reduction of Montgomery-Asberg depression scale (MASDS) at 6 weeks	Response rate: Botox 61% versus placebo 12% (P < 0.001)
					Remission rate: Botox 48% versus placebo 12% (P < 0.001)
Magid et al. 2014 [4]	Double blind, crossover*	30	28/2	50% or more reduction in HDRS score at week 6	HDRS-21 response rate: Botox 55% versus placebo 5% (P = 0.001)
					Remission rate: Botox 33% versus placebo 5%

F female, *M* Male * A cross over study is a double blind study during which patient serve as own control. The order of drug or placebo is reversed after 3–4 months in the same patients. This is unlike a parallel design study that one group of patients receive the drug, whereas anther group receive placebo

How injection of Botox into glabellar muscles (procerus and corrugator) leads to improvement of major depression is difficult to explain. One simple explanation is that improvement of frown lines makes the patients happier and happier patients are less depressed. Finzi and Rosenthal [2] have proposed that glabellar muscles, as muscles of facial expression, influence the activity of the brain cells in those areas of the brain that are involved in emotions- amygdala in the temporal lobe and prefrontal cortex (PFC) in the frontal lobe. This assumption is backed by data from functional MRI (fMRI) studies that have shown frowning following observing an unpleasant picture is associated with decreased activity of PFC and increased activity of amygdala. Antidepressant medications like paroxetine increase activity of PFC and decrease the activity of amygdala in fMRI. Functional MRI of the brain has shown that the same thing happens with Botox injection into the glabellar muscles which decreases the tone of glabellar muscles and flattens the frown lines (Fig. 17.2- lower row) [5].

Injections are done quickly with a very thin and short needle (half or ¾ inch, gauge 30) and produce minor discomfort. Most injectors do not numb the skin before Botox injections into the glabellar muscles.

Using the criteria of American Academy of Neurology, based on the current literature (3 class II studies- see Chap. 3 for definition of AAN criteria, study class, and efficacy levels), the efficacy level of Botox therapy for depression is defined as B, probably effective. So far, approximately, 90% of the studied patients have been women and all three high quality studies (Table 17.1) have been conducted with

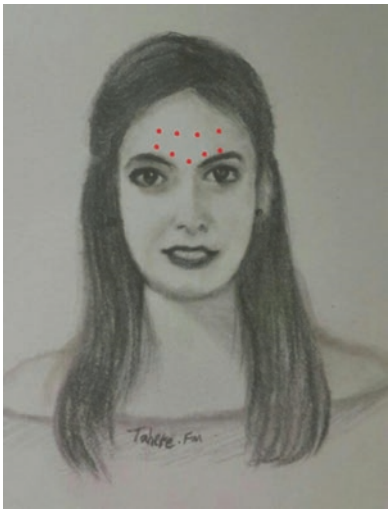

Fig. 17.2 Commonly used areas of Botox injections for glabellar lines (*lower row*) and forehead wrinkles (*upper row*). Drawing, courtesy of Dr. Tahere Mousavi

Botox. It remains to be seen if depressed men respond similarly to Botox treatment of glabellar muscles and if the same positive response can be reproduced when other type A (Xeomin and Dysport) and the type B toxin (Myobloc) are used for treatment of depression.

Cardiology (Irregular Heart Beats –Atrial Fibrillation)

The human heart has four chambers; two small ones with thin walls called atrium and two large ones with thick walls called ventricle. The two atriums are located above the ventricles and each atrium has an opening to the ventricle below it on the same side. There are valves between atria and ventricles which control the blood flow. The mitral valve is located on the left and aortic valve on the right side (Fig. 17.3).

The continuous beating of the heart (approximately 10,000 times/24 hours) is maintained through the function of a conglomeration of sympathetic and parasympathetic nerve cells called nodes (located in the left atrium) and networks of nerve cells and fibers called ganglionic plexi (GP) located in the fat pads under the surface of the heart (epicardium) around the atria. The two nodes- sinoatrial and atrioventricular (AV) work as a pacemaker for the heart; electrical impulses generated AV node travel through nerve bundles along the wall of the ventricles exciting the heart muscles. The electrical activity generated by the AV node, contracts the atria and the ventricles.

In recent years, the importance of GP as an extensive combinations of nerve cells and fibers have been emphasized with some authors describing it as a “little brain sitting over the heart” (Fig. 17.4).

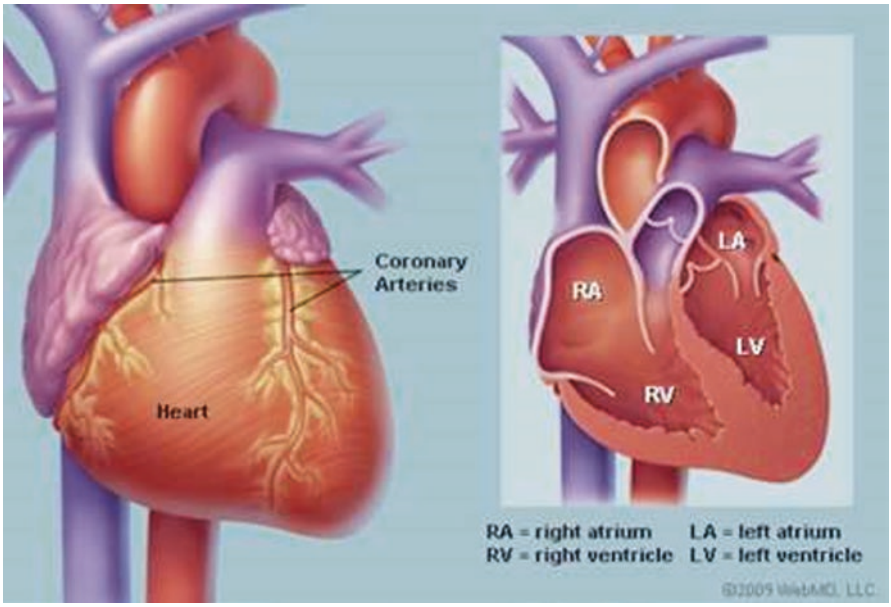

Fig. 17.3 (**a**) right: chambers of the heart and large blood vessels. (**b**) right: coronary arteries that feed the heart muscle. Printed with permission form WebMD

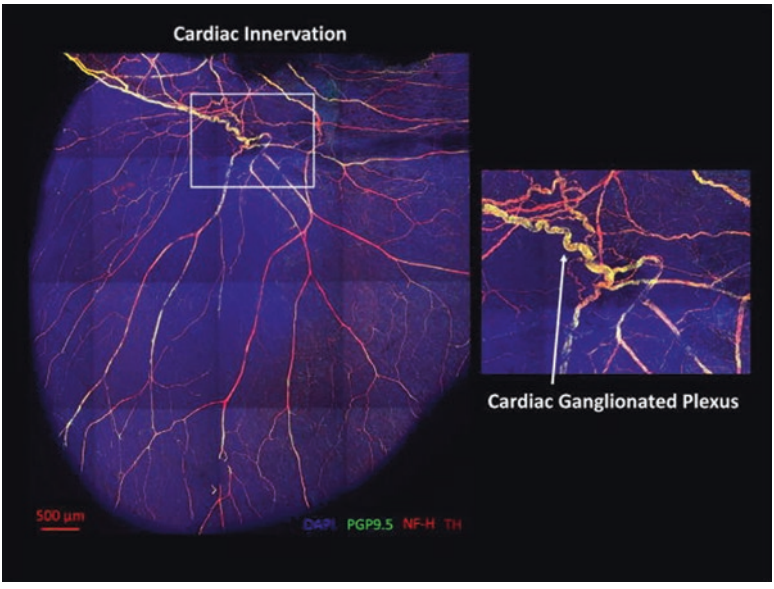

Fig. 17.4 A ganglionic plexus (nerve cell and fiber) and extensive network of nerve fibers that innervate the heart. From Buckley and co-workers in the journal of Heart Rhythm 2017. Printed with permission from publisher

Five ganglionic plexi (GP) containing sympathetic and parasympathetic cells and fibers have been identified around left and right atria embedded into the small fat pads overlaying the muscle- superior surface of the right atrium, superior surface of the left atrium, posterior surface of the right atrium, posterior medial surface of the left atrium and inferio-lateral aspects of the posterior left atrium. Abnoraml electrical activity in these sites which are often located close to the pulmonary veins can cause atrial fibrillation.

Atrial fibrillation(AF) affects 2.5% of the general population (9% or higher after age 75) and is associated with an annual stroke incidence of 5% [6]. It is characterized by irregular, fast and chaotic beating of the upper two chambers (atria) of the heart. Several factors can cause atrial fibrillation; most notable among them are high blood pressure, damage to the heart structure from coronary artery disease or myocardial infarction, abnormal thyroid function, diabetes, kidney disease and a congenital heart anomaly. The symptoms of AF include shortness of breath, palpitation (rapid heart beat) and fatigue. However, AF can be asymptomatic and suddenly present itself with stroke. Beta-blockers, calcium channel blocking agents, digoxin and thinning the blood through anticoagulation are commonly used in patients with AF for normalization of the heart rate and for prevention of stroke. Severe and recalcitrant cases of AF may respond to ablation of the AV node by high energy radio frequency pulse. Ablation of the artrio-ventricular (AV) node helps a large number of patients with AF but the procedure requires insertion of a permanent heart pacemaker.

Experimentally, researchers have produced atrial fibrillation in animals by electrical stimulation of the vagus nerve which supplies parasympathetic innervation to the heart. It has been shown that injection of botulinum toxin A (Botox) in the GP of the dog's heart can suppress AF caused by vagus nerve stimulation. Atrial fibrillation is a frequent complication of Cardiac Bypass Graft (CABG) surgery that replenishes blood supply to parts of the heart which lack sufficient blood supply. Pukoshalov and coworkers [7], investigated the effect of botulinum toxin injections into the GP of human heart in a double blind, placebo-controlled study. Prior to CABG surgery, sixty surgery candidates were randomized into toxin and saline groups (30 each). After opening the chest wall(thoracotomy), 50 units of Xeomin /1 cc or 1 cc of normal saline(placebo) was injected into each of four pericardial fat pads containing GP. During the first 30 days after surgery, 2 of 30 patients (7%) in the botulinum toxin group and 9 of 30 patients (30%) in the placebo group experienced recurrence of atrial fibrillation ($P = 0.024$). Over the next 12 months, none of the patients in the Xeomin group experienced recurrence of AF, while 7 of the 30 (27%) subjects in the placebo group had recurrences ($P = 0.002$). No patient reported any side effects. Xeomin is a Botulinum toxin type A toxin like Botox with units comparable to Botox. This is an important observation since persistent AF is a major health hazard. If the positive results of this observation (including its safety) can be reproduced by further high quality studies, BoNT injection into GPs of the heart can be a viable alternative to AV node ablation surgery which requires placement of a cardiac pacemaker.

Pain Medicine

Cancer–Related Pain

Cancer can cause pain through different mechanisms:

a) Direct local invasion of cancer to adjacent sensory nerves can cause local pain which may be severe and require potent pain medications. Anectodal observations have shown that local injection of Botox into the painful area can improve pain and quality of life.

Patient Example

A 62- years old female, an intelligent and accomplished writer with history of lung cancer, experienced severe jaw pain and stiffness of the jaw muscles that gradually locked her jaw and prevented her from eating solid food. A computed tomography scan (CT) of the head and skull showed erosion of the right jaw bone and an enlarged right masseter muscle (the masseter muscle raises the lower jaw and closes the mouth) presumably due to invasion by cancer (metastasis). Pain killers and muscle relaxants offered little help. She lost 15 pounds weight over 3 months and suffered from severe depression. Injection of Botox into the masseter muscles, 70 units in the right and 30 units in the left side relaxed the contracted muscle, unlocked the jaw and allowed eating solid food for 2 months. She also reported significant reduction of her jaw pain. Repeated Botox treatment every 2–3 months had the same effect and made the patient comfortable during the last year of her life (Fig. 17.5).

b) Local pain after cancer surgery and radiation: Many patients with head and neck, tongue or throat cancer develop persistent pain at or around the region of scar and keloid formation after surgery and radiation. Keloid is an overgrowth of the fibrous tissue over the region of skin injury, often forming an indurated scar. Several studies have shown that injection of botulinum toxins into the keloid and the surgical scars can reduce the post-surgical, post-radiation pain in patients with local cancer (specially cancers of the head and neck region).

Recently, Yale investigators have conducted two studies one with Botox and the other with Xeomin (another type of botulinum toxin A – see Chap. 3 for a list of FDA approved types of BoNTs) on patients with head, neck, throat and tongue cancer. A total of 80–120 units of Botox or Xeomin was injected into painful scars and indurated keloids, and sometimes additionally in adjacent painful muscles in either of the two studies. The patients' level of pain and quality of life was assessed at baseline, and after injection every 4 weeks for three months. In 80% of the patients, local injection of Botox or Xeomin resulted in marked reduction of local pain. Approximately half of the patients reported significant improvement of their quality of life [8, 9].

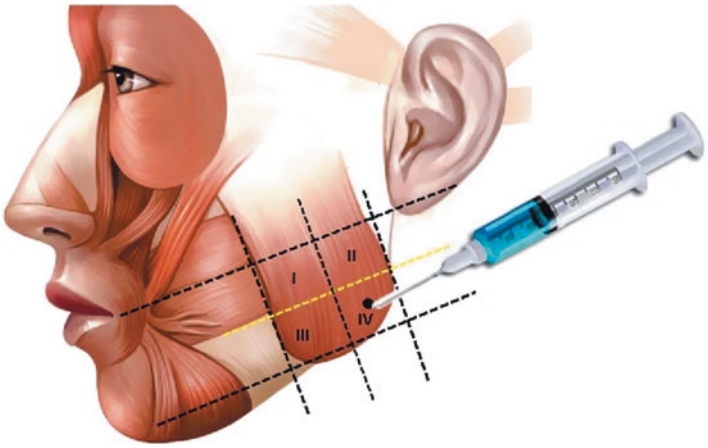

Fig. 17.5 The location of masseter muscle and how Botox injection the into the masseter is often performed. In this example 4 sites are injected. Some injectors including the author prefer two sites. From Wei and co-workers 2015. Reproduced with permission from publisher, Wolters-Kluver

Patient Example

A 48 year-old man had bilateral surgery on the neck (neck dissection), followed by neck radiation and chemotherapy for cancer of the larynx (beginning of the wind pipe in the throat). Two years, later he developed severe pain in the left side of the neck and painful spasms of the shoulder muscle (trapezius) close to the neck. Treatment with pain killers including potent agents (opioids and fentanyl), at best, provided modest relief. Injection of the anterior neck region on the left in the areas of keloid formation and left shoulder muscle close to the neck with Botox (Fig. 17.6) resulted in marked reduction of pain and improvement of the patient's quality of life. The dose for the neck injection was 10–20 units/site (Fig. 17.6) and for the shoulder was 30–40 units/site. Over a follow up period of three years, patient received injections every 4–5 months and, each time, reported satisfaction. There were no side effects.

c) Neuropathic Pain caused by Chemotherapy for Cancer.

Immune modifying drugs or drugs that are used for chemotherapy of cancer are toxic and often cause systemic complications. A painful peripheral neuropathy is common among these side effects. This form of damage to the peripheral nerves is painful, involves mainly the distal part of the limbs with the symptoms presenting most notably in the feet. The pain is a neuropathic type of pain, characterized by its sharp nature and burning quality. It can be constant and disturb sleep. We have observed that injection of Botox into or under the skin and at multiple sites with a thin needle (gauge 30) may relieve pain in patients with this type of neuropathy.

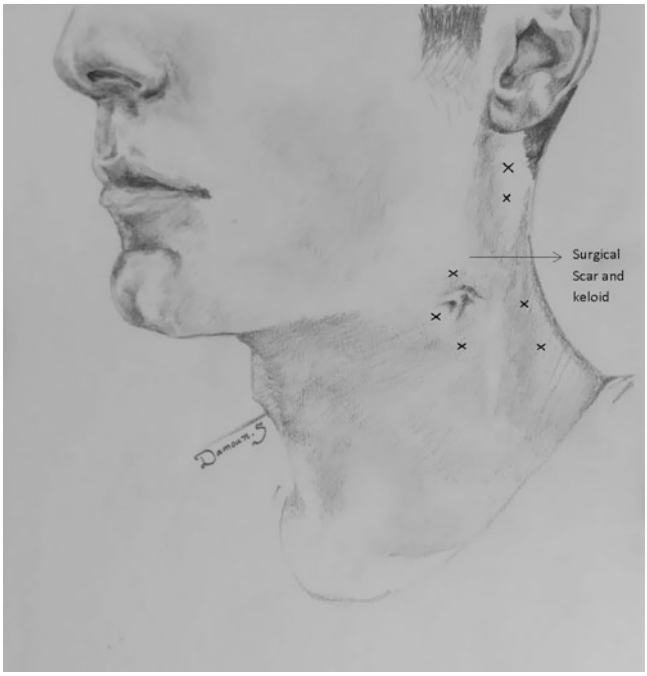

Fig. 17.6 Sites of Botox injection in the case with persistent neck and shoulder pain after surgery and radiation for throat cancer. From Safarpour and Jabbari 2018. Drawing by Dr.Damoun Safarpour. Printed with permission from Springer

Botox injections themselves are painful in these patients since their skin is sensitive, but the subsequent pain relief that lasts for months makes it acceptable to most patients.

Patient Example

A 64 year-old man complained of severe burning pain involving the top of the feet (over the big toe) and above the big toes during treatment with immune modifying agents tacrolimus and cellcept which were prescribed for management of cancer of the bone morrow. He had been diagnosed with a myeloclastic syndrome a year earlier. The pain was described as sharp, burning and unbearable at night. The most painful areas were over the big toes, on the dorsal aspect of the feet. Pain killers provided no relief. A week after injection of Botox into 10–12 sites of each affected foot (Fig. 17.7), patient reported significant pain relief that lasted for months. The Botox dose was 1.5 to 2 units/site.

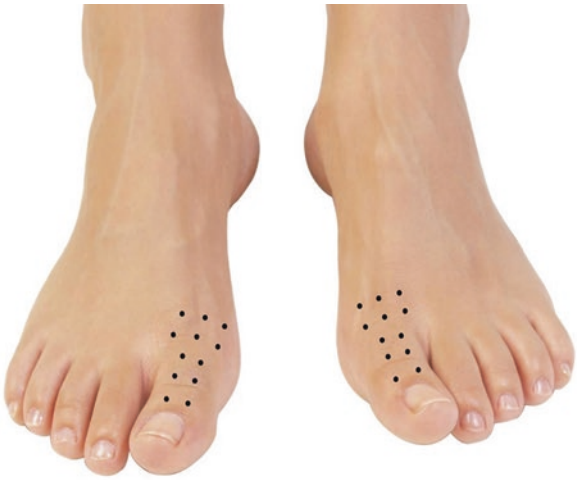

Fig. 17.7 sites of injection in the patient with cancer and neuropathic pain caused by an immune modifying drug

Prevention of Pain after Surgery

Local muscle pain along the line of excision, after organ surgery, is a common complaint. In some patients, the pain can be severe and disabling and may persist for months or years. There are several reports illustrating that local injection of Botox prevents or reduces pain after surgical procedures such as mastectomy, hernia repair, gall bladder surgery, hemorrhoidectomy, etc. Davies and coworkers conducted a careful, double blind (both physician and patient blinded to injected material) study of 50 patients who had undergone hemorrhoidectomy [10]. Injection of 20 units of Botox into the anal sphincter prior to removal of the hemorrhoids, markedly reduced postsurgical painful spasms of the anal sphincter, an effect which was statistically significant compared to placebo (saline) injection. The peak pain relief was at the sixth or seventh day after surgery.

Prevention or reduction of post-surgical pain is a major achievement of botulinum toxin therapy in the field of surgery. Further high quality studies are needed to see if this mode of treatment can be used widely and safely in the surgical field.

Temporomandibular Disorder

Temporomandibular disorder (TMD) which is characterized by pain at or around the temporomandibular joint (Fig. 17.8) affects 5–12% of the general population in US [11]. It is frequently misdiagnosed as non-specific face pain. The pain can be felt anywhere from the temples to the angle of the jaw, Most patients are not happy with conventional analgesic medications.

Despite observations by several investigators for years (most notably by Dr. Blitzer in New York) that injection of Botox can improve pain of TMD, until

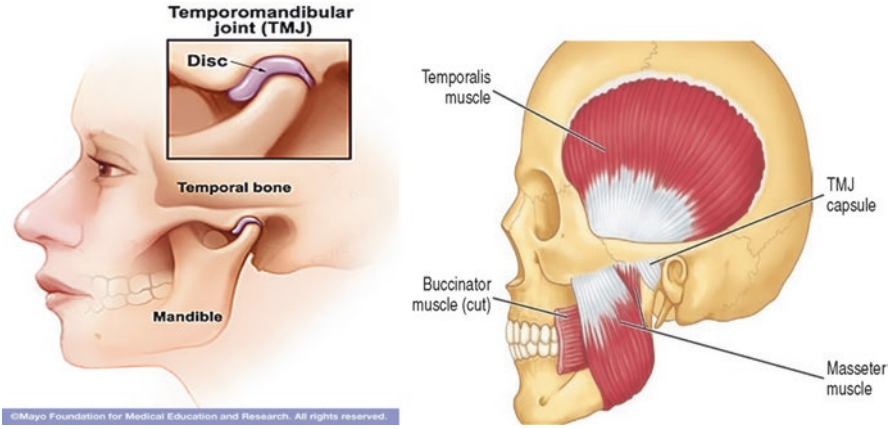

Fig. 17.8 Temporomandibular joint. Printed with permission from Mayo Foundation

recently, no high quality study was on record defining a clear technique of BoNT injection that could relieve pain in TMD. In 2017, Patel and co-workers (including Dr.Blitzer) [12] reported the efficacy of BoNT therapy in 19 patients with TMD by injecting three nearby muscles simultaneously. Their study was double blind, placebo-controlled with a parallel design (see Chap. 3 for definition of various study designs). The authors used Xemonin for this study. Ten patients received Xeomin, while 9 patients received saline (placebo). A total of 170 units was injected into three muscles: masseter 50u/side; temporalis 25u/side: and external pterygoid 10 u/side (Fig. 17.7). Xeomin is another type A botulinum toxin like Botox, with a unit potency close to that of Botox units. The level of pain was measured on a 0–10 scale, at baseline and then at 4 weeks after the injection and up to 16 weeks. At week 4 after injection, the Xeomin group demonstrated a mean reduction of pain score of 4.1 compared to 1.7 reduction observed in the placebo group. Although the placebo group also improved, most pain specialist do not consider improvements of below 2 grades (on 0–10 scale) as clinically significant. Temporalis and masseter muscles are shown in Fig. 17.7. External pterygoid muscle which is deep was not shown in this figure. It can be injected through inside of the mouth (as was done in this study) or injected externally close to the TMJ. This study has defined a technique of BoNT injection that could offer pain relief to some patients with TMD.

Teeth Grinding (Bruxism)

Bruxism is a common medical problem that can affect children and adults and presents during wakefulness or sleep. It affects up to 31% of adults [13]. Severe teeth grinding can destroy teeth, cause jaw pain and headaches. Teeth grinding during sleep interrupts sleep of both the patient and the bed partner. Medications like clonazepam (clonopin) provide modest relief, but may cause significant daytime

sedation. Several high quality studies (double blind and placebo controlled), though small in number, have demonstrated that injection of Botox into the temporalis and masseter muscles (see Fig. 17.8 for muscle locations) can improve teeth grinding. The most recent of these studies which was published in 2018 includes 23 patients with teeth grinding during sleep with 13 patients assigned randomly to Botox and 10 patients to the placebo group (blinded study) [14]. Botox was injected into temporalis muscles (40 units in each side) and masseter muscles (60 units on each side). Authors concluded that injection of Botox into those muscles safely improves teeth grinding during sleep with no significant side effects. Two patients reported transient cosmetic change in their smile. This encouraging data indicate that Botox treatment can improve teeth grinding during sleep and wakefulness without causing major or persistent side effects. Dermatology (Proriasis and recalcitrant itch): Emerging data suggests that local injection of Botox can improve recalcitrant itch and heal skin lesions in psoriasis (see Chap. 13)

References

1. Kessler RC, Berglund P, Demler, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;18(289):3095–105.
2. Wollmer MA, de Boer C, Kalak NT, et al. Facing depression with botulinum toxin: a randomized controlled trial. J Psychiatr Res. 2012;46:574–81.
3. Finzi E, Rosenthal NE. Treatment of depression with onabotulinumtoxinA: a randomized, double-blind, placebo- controlled trial. J Psychiatr Res. 2014;52:1–6.
4. Magid M, Reichenberg JS, Poth PE, et al. Treatment of major depressive disorder using botulinum toxin a: a 24-week randomized, double-blind, placebo-controlled study. Clin Psychiatry. 2014;75:837–44.
5. Hennenlotter A, Dresel C, Castrop F, et al. The link between facial feedback and neural activity within central circuitries of emotion--new insights from botulinum toxin-induced denervation of frown muscles. Cereb Cortex. 2009;19:537–42.
6. Go AS, Hylek EM. Phillips KA prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA. 2001;285:2370–5.
7. Pokushalov E, Kozlov B, Romanov A, et al. Long-Term Suppression of Atrial Fibrillation by Botulinum Toxin Injection Into Epicardial Fat Pads in Patients Undergoing Cardiac Surgery: One-Year Follow-Up of a Randomized Pilot Study. Circ Arrhythm Electrophysiol. 2015 Dec;8(6):1334–41.
8. Mittal S, Machado DG, Jabbari B. OnabotulinumtoxinA for treatment of focal cancer pain after surgery and/or radiation. Pain Med. 2012;13:1029–33.
9. Rostami R, Mittal SO, Radmand R, Jabbari B. Incobotulinum Toxin-A Improves Post-Surgical and Post-Radiation Pain in Cancer Patients. Toxins (Basel). 2016 Jan 13;8(1). pii: E22. doi: https://doi.org/10.3390/toxins8010022.
10. Davies J, Duffy D, Boyt N, et al. Botulinum toxin (botox) reduces pain after hemorrhoidectomy: results of a double-blind, randomized study. Dis Colon Rectum. 2003;46:1097–102.
11. National Institute of Dental and Craniofacial Research [7/28/2013]; Facial Pain. http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/FacialPain/
12. Patel AA, Lerner MZ, Blitzer A. IncobotulinumToxin-A for injection of temporo-mandibular joint disorder. A randomized controlled pilot study. 2017;126:328–33.

13. Mesko ME, Hutton B, Skupien JA, et al. Therapies for bruxism: a systematic review and network meta-analysis (protocol). Syst Rev. 2017;6:4. https://doi.org/10.1186/s13643-016-0397-z.
14. Ondo WG, Simmons JH, Shahid MH et al. Onabotulinum toxin-A injections for sleep bruxism: A double-blind, placebo-controlled study. Neurology. 2018 Jan 17. pii. doi: https://doi.org/10.1212/WNL.0000000000004951. [Epub ahead of print].

Index

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-319-99945-6