Bahman Jabbari

Botulinum Toxin Treatment of Pain Disorders

Second Edition

Springer

Botulinum Toxin Treatment of Pain Disorders

Bahman Jabbari

Botulinum Toxin Treatment of Pain Disorders

Second Edition

Springer

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

Clinical Professor of Neurology
University of California
Irvine, CA, USA

Editorial
Contact Carolyn Spence

ISBN 978-3-030-99649-9 ISBN 978-3-030-99650-5 (eBook)
https://doi.org/10.1007/978-3-030-99650-5

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

Dedicated to Fattaneh

Preface

Since the first edition of this book in 2015, much has developed regarding the basic and the clinical science of botulinum neurotoxin (BoNT) therapy in pain disorders. Basic scientists discovered new pain receptors upon which BoNTs exert their analgesic effects and introduced several engineered BoNT chimeras that can specifically target peripheral pain terminals as well as central neurons. Furthermore, basic scientists have shown that part of BoNT's analgesic effect is conducted via the toxins' central action. After peripheral injection of BoNT-A, the cleaved SNAP 25 can reach the spinal cord and brain stem sensory neurons through retrograde transfer and, while in the CNS, the toxin can travel from cell to cell via the phenomenon of transcytosis. Further proof for central action of the BoNT-A comes from reduction of the pain and inflammation caused by peripheral stimulation when the toxin is applied directly to the dura matter.

On the clinical side, high-quality studies have shown new areas of the toxin's efficacy such as temporomandibular pain syndrome and pain associated with bruxism. Long-term clinical trials have demonstrated continued toxin efficacy and improvement of quality of life after repeated BoNT-A injections in patients with chronic migraine as well as some other pain disorders.

This edition (second edition) consists of 20 chapters, 3 of which are new additions. There is a chapter on the history of botulinum neurotoxins. One chapter pertains to BoNT therapy in the field of dentistry and another chapter provides information on BoNT therapy for pain disorders in veterinary medicine.

I would like to thank Fattaneh Tavassoli, MD, for her editorial assistance. Drs. Tahere Mousavi, Damoun Safarpour, and Shahroo Etemad-Moghadam have kindly provided drawings for this book. I am thankful to Carolyn Spence from Springer for her continuous support and encouragement. I hope this book with its new information on BoNT therapy in pain disorders will be helpful to both clinicians and basic scientists.

I am indebted to many patients who during my 42 years of practicing medicine provided me affection and moral support. Their kindness and enthusiasm made me look into new modes of treatment both as a clinician and a researcher.

New Haven, CT, USA Bahman Jabbari
January 2022

Contents

Chapter 1
The History of Botulinum Neurotoxin Development

Introduction

The outbreaks of a disease condition characterized by muscle paralysis have been known in Germany since 1736. A German physician named Muller coined the term botulism for this illness since these outbreaks often followed consumption of spoiled sausage; in Latin, botulus means sausage. Interestingly, a much earlier reference to problems with spoiled sausage can be traced to a decree ordered by Byzantine emperor Leo the IV (750–780 AD) prohibiting citizens from eating blood sausage [1]. It was another German physician, Justinus Kerner (Fig. 1.1), who published a comprehensive description of the illness known as sausage poisoning first in 76 and then in 155 patients during the years 1820 and 1822. As a keen observer, Kerner's descriptions cover almost all symptoms that we know about botulism today, such as muscle weakness, paralysis of eye muscles, difficulty in swallowing, dry mouth, and signs of autonomic dysfunction. He followed his clinical observations with a series of animal experimentations as well as brief experiments on himself. In one observation, he reported severe dryness of the mouth after placing a small fragment of a spoiled sausage on his tongue. From his experiments, Kerner concluded that botulism developed from a potentially lethal toxin that was present in the spoiled sausage. This toxin was thought to be active in anaerobic conditions and affects mainly the motor and autonomic systems of the body, sparing the sensory system. Kerner also suggested that due to the paralytic properties of this toxin, it has potential for being used in treatment of hyperkinetic movement disorders such as chorea. In Kerner's belief, which proved to be correct years later, the culprit toxin was not prussic acid (as believed by his contemporaries), but rather a biologic toxin.

The German medical historian F.J. Erbgutt has researched and described in detail Kerner's medical accomplishments in several articles [2–4]. Kerner was also known as a good poet and was considered by Herman Hesse—the German Nobel Laureate (1946)—as one of a few true German poets of his era.

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_1

Fig. 1.1 Justinus Kerner (1786–1862)

The agent responsible for botulism was discovered by a Belgian bacteriologist, Emile Van Ermengem, in 1895 (Fig. 1.2a). On December 14, of that year, after attending a funeral, 34 Belgian musicians developed signs of botulism following consumption of spoiled ham; three of them died. Professor Ermengem, at the University of Ghent, examined the culprit ham. He was able to produce similar signs of illness in animals after injecting them with the tissue containing the toxin. On microscopic examination, the tissue obtained from dead musicians revealed anaerobic gram-positive, rod-shaped bacteria; he named the organism bacillus botulinum, believing it to be the source of the toxin in the spoiled ham (Fig. 1.2b).

In 1924, Ida Bengstrom, a Swedish-American bacteriologist, suggested to change the name of this agent from bacillus botulinum to clostridium botulinum. The word clostridium is derived from the Greek word "kloster," meaning spindle. The genus clostridia also includes anaerobic bacteria such as *Clostridium tetani*, responsible for production of tetanus toxin.

During World War II, there was interest in purifying and developing botulinum toxin (BoNT) as a weapon and finding ways to protect the soldier in case of exposure. Carl Lamanna and Richard Duff working at Fort Detrick, Maryland, a U.S. Army facility, discovered a technique to crystalize and concentrate botulinum toxin. In 1946, Edward Shantz, working at the same facility, purified and produced a large amount of the toxin. Shantz and his young colleague Erik Johnson (Fig. 1.3), at the University of Wisconsin, further refined the toxin and made it available for clinical researchers.

Fig. 1.2 (**a**) Emile Van Ermengem (1851–1932). (**b**) Clostridium botulinum

In 1949, A. Burgen and his colleagues in England discovered that the paralytic effect of botulinum neurotoxin is the result of its effect on the neuromuscular junction, through blocking the release of acetylcholine [5]. In 1964, Daniel Drachman, at Johns Hopkins University, demonstrated that injection of botulinum toxin-A into the hind limb of chicken can cause a dose-dependent muscle weakness and atrophy [6]. Drackman's work came to the attention of Allen Scott (Fig. 1.4) and his colleagues, ophthalmologists in San Francisco, CA, who were interested in improving

Fig. 1.3 Edward Shantz and Erik Johnson. From Dressler and Roggenkaemper. (Reproduced with permission from Springer)

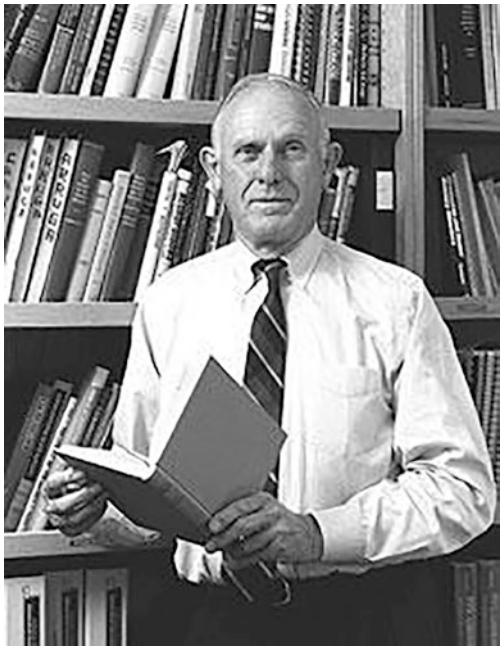

Fig. 1.4 Dr. Alan Scott who pioneered BoNT therapy in humans. (From J. Erbguth reproduced with permission from Springer)

strabismus in children. For the next decade, Dr. Scott, using Shantz's toxin, conducted several experiments in monkeys by injecting the toxin into the extraocular muscles. In 1973, he showed that injection of botulinum toxin can selectively weaken the eye muscle of the monkeys, and this selective weakening of extraocular muscles implied a potential for botulinum toxin injections to improve human strabismus. In 1980, he published the result of a clinical trial conducted on 67 patients which clearly showed that BoNT injection into selected eye muscles can indeed improve strabismus in human subjects [7]. During the 1980s, in a number of small

open-label studies, Scott and his colleagues showed that injection of BoNTs into the face can improve hyperactive face movements such as blepharospasm and hemifacial spasm. Scott was also first to show that injection of 300 units of onabotulinumtoxinA (then called oculinum) in a single session (for spasticity) is safe, a safety margin that was not known prior to his observation [8].

These observations were of great interest to movement disorder specialists and led to conduction of several small blinded protocols by US (Fahn, Jankovic, Brin, and others) and Canadian (Tsui and others) investigators that ultimately resulted in FDA approval of botulinum toxin-A in 1989 for blepharospasm, hemifacial spasm, and strabismus (mainly based on Scott's work) (Table 1.1).

The initial name of oculinum used in earlier studies was changed to Botox 2 years later when Allergan Inc. acquired the right of distribution and marketing of the toxin.

Along these clinical developments, our knowledge about the molecular structure of the toxin and where and how it works improved significantly through the tireless efforts of biologists and basic scientists; the contributions of some of them are described briefly at the end of this chapter (Fig. 1.5).

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

Year	Investigator(s)/FDA approvals	Comment
1820–1822	Justinus Kerner	Described details of botulism; predicted that the toxin can be used in the future as medical remedy
1895	Emile van Ermengem	Discovery of bacteria causing botulism
1944–1946	Lamanna and Duffy	Concentrated and crystalized the toxin
1946	Edward Schantz	Purified and produced the toxin in a form suitable for medical research
1949	A. Burgen	Acetylcholine identified as the chemical blocked by BoNT at nerve muscle junction
1953	Daniel Drachman	Intramuscular injection of Schantz's toxin can be quantified and caused dose-dependent muscle weakness in chicks.
1973	Alan Scott	Injection of type A toxin improved strabismus in monkeys
1980	Alan Scott	Controlled human study showed efficacy in strabismus. Observations on potential use for blepharospasm, hemifacial spasm, and spasticity
1985–1988	Fahn, Jankovic, Brin, Tsui	Controlled and blinded studies showed efficacy in blepharospasm and cervical dystonia
1989	FDA approval of type A toxin (oculinum—Name later changed to Botox)	Toxin approved for use in blepharospasm, hemifacial spasm, and strabismus
1989–present	FDA-approved several other indications	Toxin approved for facial wrinkles, frown lines, cervical dystonia, chronic migraine, bladder dysfunction, upper and lower limb spasticity, and axillary sweating

Fig. 1.5 Dr. James Rothman, Yale cell biologist who won the Nobel Prize in 2013 for his work on Synapse physiology. His laboratory purified the SNARE complex, the synaptic protein targeted by botulinum toxin

What happened next is one of the most amazing developments in clinical pharmacotherapy. A feared and lethal toxin was shown to be effective and relatively safe for treatment of a large number of medical conditions [9]. More recently, its use has been extended to the field of dentistry and veterinary medicine (Chaps. 16 and 19 of this book). Other botulinum neurotoxinAs (incobotulinumtoxinA and abobotulinumtoxinA) and BoNT-B (rimabotulinumtoxinB) have been found to be effective in several medical and surgical conditions as well (Table 1.2). Newly developed botulinum toxins such as Korean toxin Meditox and Chinese toxin (Prosigne) have also shown promise in a number of neuropathic pain conditions [10]. A new form of botulinum toxin A (PrabotulinumtoxinA—Jeuveau) recently received approval for treatment of frown lines in the United States. Chapter 3 of this book describes the characteristics of available and marketed botulinum toxins as well as their similarities and differences. The list of US-marketed botulinum neurotoxins, their clinical indication, and the year of FDA approval for each indication is presented in Table 1.2.

This brief account of botulinum toxin history will not do justice to the subject if it did not include significant contribution of recent contemporary basic scientists and clinical neurotoxicologists who have been instrumental in the current status of BoNT therapy (2022). Some of the most influential individuals in this field are presented below. The list is by no means complete.

Table 1.2 Clinical indications (approved by the FDA) for botulinum toxins marketed in the United States

Generic and trade names	Abbreviation	Manufacturer	Approved indication (FDA)	Year of FDA approval
OnabotulinumtoxinA; Botox	onaBoNT-A	Allergan Inc., Dublin, Ireland	Blepharospasm	1989
			Hemifacial spasm	1989
			Strabismus	1989
			Cervical dystonia	2000
			Glabellar lines	2002
			Axillary hyperhidrosis	2004
			Chronic migraine	2010
			Upper limb spasticity	2010
			Neurogenic bladder	2011
			Lateral canthal lines	2013
			Overactive bladder	2013
			Adult lower limb spasticity	2016
			Forehead lines	2017
			Pediatric upper limb spasticity	2019
IncobotulinumtoxinA; Xeomin	incoBoNT-A	Merz Pharma GmbH & Co., Frankfurt, Germany	Cervical dystonia	2010
			Blepharospasm	2010
			Glabellar lines	2011
			Adult upper limb spasticity	2015
			Sialorrhea	2018
AbobotulinumtoxinA; Dysport	aboBoNT-A	Ipsen Pharmaceutical, UK	Cervical dystonia	2009
			Glabellar lines	2009
			Adult upper limb spasticity	2015
			Pediatric lower limb spasticity	2016
			Adult lower limb spasticity	2017
			Wrinkles	2019?
RimabotulinumtoxinB; Myobloc/Neurobloc	rimaBoNT-B	US World Med-Solstice	Cervical dystonia	2009
			Sialorrhea	2010
PrabotulinumtoxinA; Jeuveau	praboBoNT-A	Evolus Inc., Santa Barbara, CA	Frown lines	2019

Biology and Basic Science

James E. Rothman, PhD, chairman of the Department of Cell Biology at Yale University, revolutionized the field of cell biology by studying the molecular processes in a cell-free system. His work discovered many genetic and functional aspects of synapse physiology including vesicular trafficking, vesicular fusion, and proteins involved in this function. He identified genes and enzymes responsible for the budding of vesicles and their fusion with membranes. Dr. Rothman's laboratory succeeded in the purification of the SNARE complex and provided pivotal evidence for establishing the central role of the SNARE complex (proteins targeted by botulinum toxins) in mediating membrane fusion. In 2013, Dr. Rottman was awarded the Noble Prize in Medicine and Physiology.

Cesare Montecucco's first seminal work on BoNTs was the proposal of the double-receptor model in 1986, which is now well established for the majority of BoNTs. In 1992, he demonstrated that the common belief that the opposite symptoms of botulinum and tetanus toxins (flaccid versus spastic paralysis, respectively) are induced by different molecular actions is incorrect. In fact, the cleavage of a single protein is essential for the function of both toxins. The opposite symptoms are simply due to the different neurons targeted by tetanus and botulinum neurotoxins: the inhibitory interneurons of the spinal cord and the peripheral cholinergic neurons, respectively [11]. This was a major breakthrough in the understanding of the molecular pathogenesis of these diseases.

Giampietro Schiavo with a series of pioneering experiments, together with Cesare Montecucco, demonstrated that the inhibition of synaptic activity caused by tetanus and botulinum neurotoxins is due to a specific protease activity [12]. He showed that these neurotoxins cleave three synaptic proteins that play fundamental roles in neurotransmitter release. This discovery was instrumental for the field of SNARE biology and generated great interest worldwide. The seminal discovery of SNARE proteins as the substrates for BoNTs and TeNT in the early 1990s, led by Giampietro Schiavo and Cesare Montecucco, along with the groundbreaking work from James Rothman's laboratory on the purification of the SNARE complex provided pivotal evidence for establishing the central role of the SNARE complex in mediating membrane fusion.

Matteo Caleo's research on botulinum neurotoxins was devoted to their central effects. In collaboration with Cesare Montecucco in Padua and Giampietro Schiavo in London, he demonstrated that BoNTs are retrogradely transported from the injected muscle along the axons of motor neurons and directly affect neurotransmission in central areas [13].

Ornella Rossetto's collaboration with Prof. Montecucco and Prof. Giampietro Schiavo led to the discovery of the zinc-endopeptidase activity of tetanus and botu-

linum neurotoxins and provided initial experimental evidence that the molecular basis of their exceptional specificity is based on a double recognition of the substrate, i.e., of the cleavage site and of other regions outside the cleavage site termed SNARE motif.

Zdravko Lackovic, chairman of Department of Pharmacology in Zagreb, Croatia, along with his colleagues **Ivica Matak**, **Lidjia Back-Rojecky**, **and Boris Filipovic**, through a series of elegant experiments, provided strong evidence for the central action of botulinum toxins in the pain pathways [14, 15]. Their findings have improved our knowledge about the central analgesic mechanisms of botulinum neurotoxins in pain. Their contributions to this field have opened the path and encouraged many clinical neurotoxicologists to conduct controlled clinical trials in different pain disorders.

Oliver Dolley, Research Professor and Director of the International Center for Neurotherapeutics (ICNT) in Dublin, has done multidisciplinary investigations on the molecular basis of communications in the nervous system searching for proteins responsible for the fundamental process of transmitter release and its indirect regulation of voltage-sensitive K+ channels. His investigations have provided important information on endocytosis of botulinum neurotoxins by glutamatergic and peptidergic neurons. His most recent work has focused on selective targeting of sensory neurons by different agents to achieve analgesia. He has been successful in producing analgesia in rats by using a novel A/E toxin chimera [16].

Pietro De Camilli, MD, PhD.
Dr. De Camilli is professor of Neuroscience and cell biology at Yale University and founding Director of the Yale Program in Cellular Neuroscience, Neurodegeneration, and Repair. His research has provided insight into mechanisms of membrane fission and has revealed ways through which membrane-associated proteins can generate, sense, and stabilize lipid bilayer curvature. His discovery and characterization of the role of phosphoinositide metabolism in the control of endocytosis have broad implications in the fields of phospholipid signaling and membrane traffic. Dr. De Camilli and his collaborators were to first to discover that the synapse protein targeted by BoNT-A is SNAP-25 [17].

Neurologists: Clinical Neurotoxicologists in the United States

Joseph Jankovic, MD.
Joseph Jankovic, MD, Professor of Neurology at Baylor College of Medicine, is probably the most influential clinician/neuroscientist in discovering and promoting different clinical indications for the use of botulinum neurotoxins in medicine. He has contributed, often as a leader, in many well-designed clinical trials with botulinum toxins for different indications. His rating scale for blepharospasm is widely

used, especially in clinical trials of botulinum toxins. He is an outstanding teacher, who over the years has trained many fellows and young physicians for proficiency in botulinum toxin treatment. As a prolific writer, his list of publications in Medline as of December first, 2021, includes 198 articles on the subject of botulinum neurotoxins. Dr. Jankovic has held many important positions in national and international toxin-related forums. He is the recipient of life-time achievement award at the International Toxin Conference in 2018.

Mark Hallett, MD.
Dr. Mark Hallett is the Director of the Division of Movement Disorder and Motor Control in NINDS, National Institutes of Health in Bethesda, Maryland. As an internationally renowned figure in the field of movement disorders and clinical neurophysiology, Dr. Hallett has provided evidence that intramuscular injection of botulinum toxins changes the electrophysiology of muscle, peripheral nerves, and central nervous system. Under his supervision, botulinum toxin treatment of movement disorders developed at NIH; young and brilliant faculty members such as Leonard Cohen, Barbara Illowky Karp, Cordin Lungu, and Kathrine Alter developed expertise in different areas of their interest and rose to the level of international experts in this field. His group conducted the most comprehensive studies of BoNT therapy in task-specific dystonias (Medline articles related to BoNTs as of December 1, 2021: 66). He is the recipient of life-time achievement award at the International Toxin Conference in 2017.

Michell Brin, MD.
Dr. Brin was trained under Stanley Fahn, MD, at Columbia University, NY, and conducted some of the earliest studies of onabotulinumtoxinA efficacy in movement disorders (mostly tremor and dystonia). Over the past 30 years, he has been a key investigator in a large number of clinical trials. As an executive at Allergan Inc., he has been a key player in FDA approval of onabotulinumtoxinA for several clinical conditions (migraine, spasticity, cervical dystonia, and axillary hyperhidrosis) (Medline articles related to BoNTs as of December 1, 2021:110).

Cynthia Comella, MD.
Professor of Neurosurgery and Neurological Sciences at Rush Medical School, Chicago, Ill, Dr. Comella has been a major contributor and investigator in several multicenter studies conducted on botulinum toxin therapy in the United States. Her major area of work has focused on the investigation of the effect of botulinum toxins in cervical dystonia. Through her efforts and those of her collaborators, all four marketed BoNTs in the United States received approval by the FDA for U.S. use in cervical dystonia. As an expert electromyographer, Dr. Comella defined precise injecting methods to target difficult neck muscles in cervical dystonia. Her educational workshops in the annual meetings of the American Academy of Neurology are popular and well received (Medline articles related to BoNTs as of December 1, 2021: 57).

David M. Simpson, MD.
David M. Simpson, MD, FAAN, is Professor of Neurology at the Icahn School of Medicine at Mount Sinai, Department of Neurology. He is Director of the Neuromuscular Diseases Division and the Clinical Neurophysiology Laboratories. His main area of focus has been on the study of BoNTs efficacy in spasticity. He and his colleagues have shown, in an important study, that up to 800 units of incobotulinumtoxinA in one session can be used for treatment of poststroke spasticity without serious side effects [18]. He is the chair of the Guidelines and Assessment Subcommittee of AAN that periodically assesses the efficacy of BoNTs for different neurological disorders (Medline articles related to BoNTs as of December 1, 2021: 36).

Daniel Troung, MD.
Dr. Truong has been a major contributor to multicenter studies on cervical dystonia and blepharospasm. His book *Manual of Botulinum Toxin Therapy* has been received with enthusiasm worldwide due to its practical points delivered with remarkable anatomical drawings. The book has been translated into many languages (Medline articles related to BoNTs as of December 1, 2021: 42).

Bahman Jabbari, MD.
Bahman Jabbari, professor emeritus of Neurology at Yale University, started his practice and research on BoNT therapy in 1990 by establishing a comprehensive BoNT therapy clinic at Walter Reed Army Medical Center, Washington, D.C. and 15 years later at Yale University School of Medicine in New Haven, CT. He and his colleagues were the first to show the efficacy of BoNT therapy in plantar fasciitis and in nonsurgical low back pain. His most recent contribution is designing a special Electromyography (EMG)-guided method that can significantly reduce the incidence of hand and finger weakness after BoNT injection into the forearm muscles of patients with Parkinson's tremor and essential tremor. Dr. Jabbari is the author of two books on botulinum toxin therapy and editor of two additional books on the same subject (Medline articles related to BoNTs as of December 1, 2021: 46).

PREEMPT Group (Drs. Silberstien, Dodick, Aurora, Lipton, Blumenfeld, and Others)

A group of investigators, expert in treatment of headache, demonstrated the efficacy of onabotulinumtoxinA injections in chronic migraine [19] through two well-designed, multicenter, blinded clinical trials (PEEMPT I & II), that led to its FDA approval in 2010. Subsequently, in a series of articles, using the large PREEMPT cohort, they have shown that BoNT therapy in chronic migraine also improves the patients' quality of life and is effective in migraineurs with medication overuse. BoNT therapy is now an established treatment for chronic migraine worldwide.

Germany

Dirk Dressler, MD.
Dr. Dressler, director of Division of Movement Disorders at the University of Hanover, Germany, is probably the most influential clinical neurotoxicologist and clinical toxin researcher in Europe. He developed an interest in BoNT therapy during his training with late David Marsden at the National Hospital of London (1980s). He was the first person who organized BoNT therapy in Europe and is the individual with most clinical toxin-related publications in the European continent [20]. Dr. Dressler is the author of two books on botulinum toxin therapy, the first one in German and the second in English.

Reiner Benecke, MD.
Dr. Benecke, like Dr. Dressler, developed his interest in clinical use of botulinum neurotoxins while working with Dr. Marsden's group in London. Dr. Benecke and Dr. Dressler participated in the development of incobotulinumtoxinA (Xeomin), then called NT201 (in research protocols), during their several years of partnership in Rostock, Germany. Their publications on merits of incobotulinumtoxinA as a BoNT free of neutralizing proteins and on immunology of botulinum neurotoxins paved the way for extensive use of this form of BoNT-A in Europe and the United States. The list of other German physicians with expertise in botulinum toxin therapy and significant contributions to this field includes (but is not limited to) Wolfgang Jost, Gerhard Reichel, Markus Naumann, Jorg Wissel, and Fereshteh Adib Saberi.

Austria

Werner Poewe, MD.
Professor Poewe is the chairman of Department of Neurology at the Medical University of Innsbruck, Austria. He conducted several clinical trials assessing the efficacy of BoNTs in different movement disorders and spasticity. In an early study, he showed that in children and young adults, 200 units of onabotulinum injected per leg is relatively safe and is more effective than a lower dose of 100 units. He served as president of the International Movement Disorder Society from 2000 through 2002 and as President of the Austrian Society of Neurology from 2002 to 2004. He is the author of a book entitled *Botulinum Toxin Treatment in Cerebral Palsy* (Medline articles related to BoNTs: 38).

This chapter has provided a brief summary of events and individuals who paved the way for the present use of BoNTs in the management of various clinical ailments including pain disorders.

References

1. Whitcup SM. The history of botulinum toxins in medicine: a thousand year journey. Handb Exp Pharmacol. 2019. https://doi.org/10.1007/164_2019_271.
2. Erbguth FJ. Botulinum toxin, a historical note. Lancet. 1998;351(9118):1820. https://doi.org/10.1016/S0140-6736(05)78793-6.
3. Erbguth FJ. Historical notes on botulism, Clostridium botulinum, botulinum toxin, and the idea of the therapeutic use of the toxin. Mov Disord. 2004;19(Suppl 8):S2–6. https://doi.org/10.1002/mds.20003.
4. Erbguth FJ. From poison to remedy: the chequered history of botulinum toxin. J Neural Transm (Vienna). 2008;115(4):559–65. https://doi.org/10.1007/s00702-007-0728-2.
5. Burgen AS, Dickens F, Zatman LJ. The action of botulinum toxin on the neuro-muscular junction. J Physiol. 1949;109(1–2):10–24. https://doi.org/10.1113/jphysiol.1949.sp004364.
6. Drachman DB. Atrophy of skeletal muscles in chicks embryo treated with botulinum toxin. Science. 1964;145(3633):719–21. https://doi.org/10.1126/science.145.3633.719.
7. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. J Pediatr Ophthalmol Strabismus. 1980;17(1):21–5.
8. Scott AB. Development of botulinum toxin therapy. Dermatol Clin. 2004;22(2):131–v. https://doi.org/10.1016/s0733-8635(03)00019-6.
9. Jankovic J. Botulinum toxin: state of the art. Mov Disord. 2017;32(8):1131–8. https://doi.org/10.1002/mds.27072.
10. Jabbari B. Botulinum toxins in pain disorders. Springer; 2015.
11. Schiavo G, Benfenati F, Poulain B, et al. Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin. Nature. 1992;359(6398):832–5. https://doi.org/10.1038/359832a0.
12. Schiavo G, Rossetto O, Santucci A, DasGupta BR, Montecucco C. Botulinum neurotoxins are zinc proteins. J Biol Chem. 1992;267(33):23479–83.
13. Caleo M, Spinelli M, Colosimo F, et al. Transynaptic action of botulinum neurotoxin type A at central cholinergic boutons. J Neurosci. 2018;38(48):10329–37. https://doi.org/10.1523/JNEUROSCI.0294-18.2018.
14. Filipović B, Matak I, Bach-Rojecky L, Lacković Z. Central action of peripherally applied botulinum toxin type A on pain and dural protein extravasation in rat model of trigeminal neuropathy. PLoS One. 2012;7(1):e29803. https://doi.org/10.1371/journal.pone.0029803.
15. Matak I. Evidence for central antispastic effect of botulinum toxin type A. Br J Pharmacol. 2020;177(1):65–76. https://doi.org/10.1111/bph.14846.
16. 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. https://doi.org/10.1016/j.neuropharm.2017.03.026.
17. Blasi J, Chapman ER, Link E, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. Nature. 1993;365(6442):160–3. https://doi.org/10.1038/365160a0.
18. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6):921–36. https://doi.org/10.1111/j.1526-4610.2010.01678.x.
19. 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(14):1321–8. https://doi.org/10.1212/WNL.0000000000003789.
20. Dressler D, Roggenkaemper P. A brief history of neurological botulinum toxin therapy in Germany. J Neural Transm (Vienna). 2017;124(10):1217–21. https://doi.org/10.1007/s00702-017-1762-3.

Chapter 2
Molecular Structure, Mode of Action, Immunology, Safety, and Side Effects of BoNTs

Introduction

This chapter describes the molecular structure of botulinum neurotoxins (BoNTs), the intricacies of its mode of action on cholinergic synapses, the immunological aspects of BoNTs, and the safety profile of botulinum neurotoxins.

Structure of Botulinum Neurotoxin and Its Mode of Action

Botulinum neurotoxin (BoNT) is produced by clostridium botulinum, a gram-positive anaerobic bacillus that is widely present in nature. There are now eight serotypes of BoNTs designated as A, B, C, D, E, F, G, and X. In recent years, several subtypes have been described such as A1, A2, A3… for the A serotype [1]. Among these serotypes, only types A, B, C, D, and F cause botulism in humans. The source of infection is usually contaminated food as the spores of these bacteria can survive for a long time in the environment. Although each serotype has a distinct molecular structure, there is significant homology between different toxins as well as between BoNTs and tetanus toxin [2].

Currently, only serotypes A (A1) and B are used in clinical practice. After intramuscular injection, these serotypes exert their therapeutic action within a few days which usually lasts for 3–4 months. Serotype E has a faster onset (usually within 24 h) and shorter duration of action (2–4 weeks); the latter may be desirable for analgesic indications [3].

Botulinum neurotoxin complex is composed of a toxin core with a molecular weight of 150 kDa, a size that is constant among different toxin serotypes. The toxin is embedded into a larger nontoxic protein complex, the size of which varies among different toxins; for instance, it is 900 kDa for onabotulinumtoxinA (botox) and

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_2

700 kDa for rimabotulinumtoxinB (Myobloc). This protein protects the toxin when exposed to deactivating factors such as stomach acid, high temperature, and proteases. The nontoxic protein complex (NAPS) includes hemagglutinin proteins (HA proteins) and non hemagglutinin proteins. The non-hemagglutinin protein part of the protein complex includes specific antigenic proteins which are the source of antibody formation against the toxin after BoNT therapy.

The core toxin is composed of a heavy chain (HC) and a light chain (LC); the two chains are linked by a single disulfide bond. The light chain has one domain (catalytic domain) and is the active moiety of the toxin; its function is exerted inside the cell and on a specific set of proteins (SNARE proteins) through a zinc-activated protease. The heavy chain has two distinct domains HC and HN. These domains help the toxin molecule attach itself to cell membrane (end of peripheral axon, HC-binding domain), enter the peripheral nerve terminal, and later free the light chain from the core toxin structure in order for it to exert its catalytic function (translocation domain HN).

In clinical practice and for most indications, botulinum toxins are introduced through intramuscular injection; for some pain indications, they are injected subcutaneously, however. After injection, within minutes, the core toxin disassociates itself from the surrounding protein complex and is activated (nicked) [4]. The type A toxin is naturally activated by its own protease [5], whereas activation of other BoNTs takes place by exposure to the tissue proteases. After activation, the toxin quickly reaches the peripheral synapses of cholinergic neurons probably through lymphatics or blood. There, the toxin blocks the release of acetylcholine from presynaptic vesicles through five intricate sequential steps:

1. Receptor binding: Upon reaching the cholinergic synapse (neuromuscular junction or autonomic synapse), the HC domain (binding domain) of the toxin's heavy chain (Fig. 2.1) attaches the core toxin complex to two specific cell membrane receptors, namely, ganglioside and synaptic vesicle (SV) receptors [1, 6, 7]. The polysialoganglioside (PSG) receptor is abundant on the presynaptic membrane. The SV is present on the wall of synaptic vesicles (Fig. 2.2). This dual attachment is believed to be important since attachment to PSG receptor facilitates attachment of the toxin to SV receptor, which acts as a channel to let the toxin to endocytose and reach inside the presynaptic part of the cholinergic axon [8]. BoNTs A and B attach to different segments of SV receptor. The type A toxin attaches to the region known as SV2 which is a glycoprotein. The SV attachment site for type B toxin is called synaptotagmin (Syt1/Syt2) and contains calcium sensors (Fig. 2.2).
2. Internalization: After entry into the cell (presynaptic part of the axon), the toxin is visualized mainly inside presynaptic vesicles (mouse model).
3. Translocation: Inside the presynaptic vesicles is an acidic milieu caused by a specific proton pump that keeps a PH gradient across vesicle membrane in order to move the neurotransmitters into the vesicle. This acidic environment weakens the HC bond of the toxin resulting in the formation of a translocation channel that moves the light chain of the toxin from inside of the vesicle to the side of the ves-

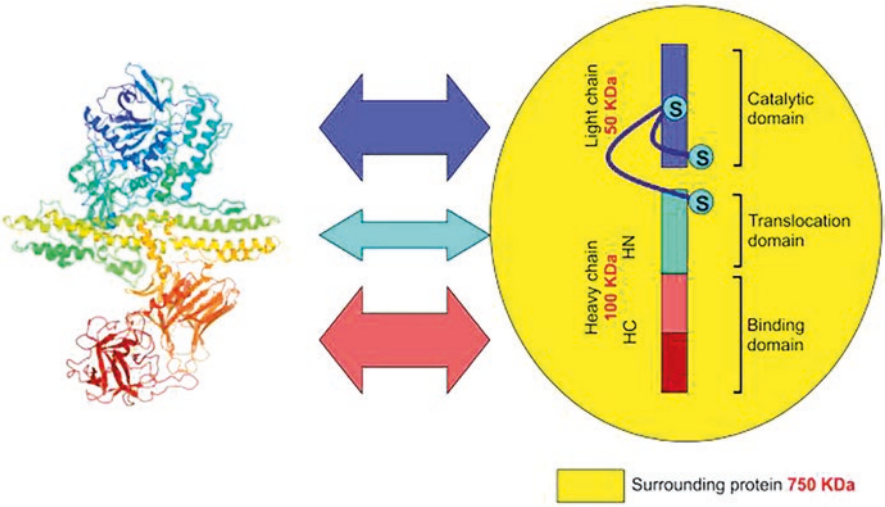

Fig. 2.1 The molecular structure of botulinum toxin. From Choudhury et al., Botulinum Toxin. An update on pharmacology and newer product developments. Toxins, 2021. Reproduced under creative commons distribution. Courtesy of PMC and Toxins

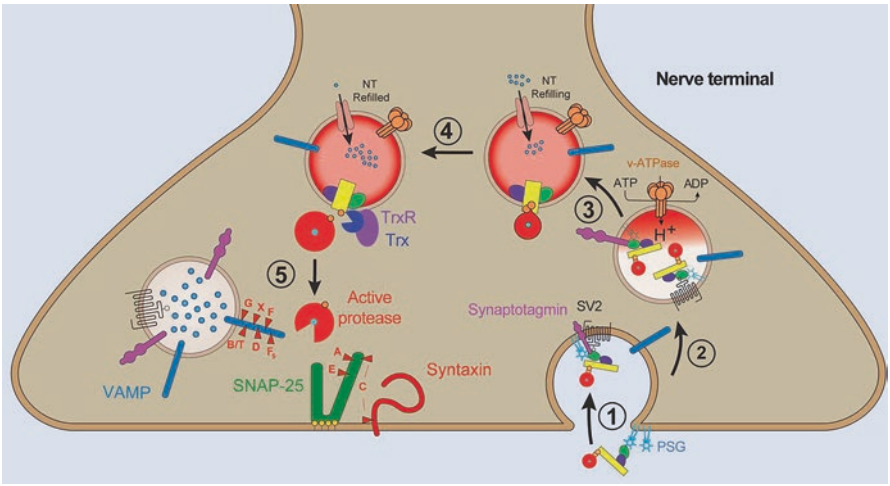

Fig. 2.2 Mechanisms of action of BoNTs. From Rossetto O, Pirazzini M, Fabris F, Montecucco C. Botulinum Neurotoxins: Mechanism of Action. Handb Exp Pharmacol. 2021;63:35–47. Reproduced with permission of publisher (Springer)

icle membrane facing the cytosol. The partially unfolded light chain and disulfide bond between two chains are now subject to the function of cytosolic enzymes.

4. Reduction of disulfide bond: At this stage, the disulfide bond that connects HC and LC is reduced and broken releasing the light chain into the cytosol to target SNARE proteins. The cytosolic enzyme that performs this function is NADPH–Thioredoxin reductase–thioredoxin system. It has been shown in animals that inhibition of this enzyme can prevent BoNT intoxication [9].
5. Cleavage of SNARE proteins by the light chain of BoNT: SNARE proteins are a set of proteins that are present in cholinergic synapses, and their function is to fuse the synaptic vesicles to the membrane of the nerve terminal, causing its rupture and release of the neurotransmitter into the synapse. The light chain of botulinum toxin, via its zinc-activated protease, inactivates SNARE proteins, hence preventing vesicle fusion and neurotransmitter release. BoNTs A and E cleave the SNARE protein named SNAP25 which is located on the nerve terminal membrane, whereas BoNTs B, D, F, and G cleave SNARE protein VAMP which is located on the vesicle membrane itself (Fig. 2.2). Inhibition of SNARE proteins in the neuromuscular synapses results in muscle paralysis, and in autonomic synapses, causes loss of gland secretions (saliva, tear). The effect on pain transmitters is discussed in the next chapter (Chap. 3) of this book. Since the action of light chain's protease is zinc dependent and zinc deficiency is not uncommon in western countries, it has been suggested that adding zinc to the dietary regimen (especially when zinc deficiency is suspected) might enhance the therapeutic efficacy of BoNTs [10].

Currently, four types of BoNTs are used widely in clinical practice with the following FDA designations and trade names:

- OnabotulinumtoxinA (onaA)—Trade name: Botox, Allergan Inc., Irvine, CA.
- AbobotulinumtoxinA (aboA)—Trade name: Dysport, Ipsen Biopharm LTD, Wrexham, UK.
- IncobotulinumtoxinA (incoA)—Trade name: Xeomin, Merz Pharmaceuticals LLC, Greensboro, NC.
- RimabotulinumtoxinB (rimaB)—Trade name: Myobloc in the United States and Neurobloc in Europe, Solstice Neurosciences, Inc., San Francisco, CA.

OnaA is provided in vials of 50, 100, and 200 units, incoA in vials of 50 and 100 units, aboA in vials of 300 and 500 units, and RimaB in vials of 2500, 5000, and 10,000 units. A newly FDA-approved toxin (2019) for dermatological indication (glabellar lines), prabotulinumtoxinA (Jeuveau), is provided in vials of 100 units. Although, as emphasized by FDA, units of various BoNTs are not interchangeable, in randomized comparator clinical trials (RCTs), an approximate unit equivalence is sometimes used (1 onaA unit = 1 incoA = 2.5–3 aboA = 40–50 units of rimaB).

All FDA-approved type A toxins (onaA, aboA, incoA, and praA) need to be diluted with preservative-free saline before use. The commonly used dilutions are in 1–2 cc of 0.9% saline. AbotulinumtoxinA was initially approved for 1 cc dilution, but a recent study has proven that 2 cc dilution is also effective [11]. RimabotulinumtoxinA is provided in an already diluted form per vial. Among these

toxins, incoA does not need refrigeration, but all other toxins do. After mixing, gentle shaking is recommended for onaA, but inverting the vial is not recommended for incoA, and the manufacturer recommends gentle shaking and multiple inversions of the vial. All manufactures recommend using the prepared solution of the toxin within 4–24 h after mixing the powder inside of the vial with saline. Liu et al. [12], however, have shown that prepared solution of onabotulinumtoxinA kept up its efficacy up to 6 weeks if kept refrigerated at 39.2°F (4 °C); if frozen, its efficacy lasted up to 6 months. Structure, formulation, pharmacokinetic, and pharmacological properties of botulinum neurotoxins are presented in Table 2.1 [13].

Diffusion and Spread of Neurotoxins

Ramirez-Castaneda et al. [13] have provided a detailed review of diffusion, spread, and migration of the botulinum neurotoxins. Overall, their conclusion was that in most clinical conditions, the diffusion of the toxin is limited, a factor that accounts for its relative safety in clinical practice.

A variety of factors could potentially influence diffusion of the injected BoNTs into the adjacent muscles. The total dose, number of injected sites, volume of injected solution, type of toxin, state of muscle pathology, and status of muscle activity after injection are all potential contributors to the extent of toxin diffusion. Detailed information about these factors is still scarce and evolving, however. Although several studies indicate that local injection of the BoNTs causes abnormal electrophysiological changes in distant and even sometimes contralateral muscles [14–16], these changes do not seem to have meaningful clinical implications since significant weakness of distant muscles rarely occurs after local injection and contralateral weakness has not been convincingly documented in clinical settings.

Animal studies suggest that the extent of diffusion after BoNT injection is dose dependent. In one study [17], injection of 1 unit of onaA into longissimus dorsi muscle of the rabbit demonstrated marked reduction of diffusion gradient beyond 15–30 mm from the site of injection, whereas injection of 5–10 units caused an effect within the entire muscle. The extent of diffusion in this study was defined through acetylcholine esterase staining. As the four commonly used neurotoxins in the United States and Europe (onaA, aboA, incoA, and rimaA) have different molecular sizes (Table 2.1), one would think that toxins with smaller molecular weight (for instance, incoA with total 150 kDa and practically no additional protein) would diffuse more readily and more extensively in the injected tissue. A study in mice, however, has demonstrated that all three type A toxins (onaA, aboA, and incoA) possess a very similar diffusion pattern, regardless of their molecular weight, after injection into the tibialis anterior muscle; most of the toxins remained close to the site of the injection and did not spread to the adjacent muscles [18]. The investigators used neural cell adhesion molecule (N-CAM) as a measure of BoNT diffusion. This molecule is present in embryonic muscle tissue but disappears in adult

Table 2.1 Properties of botulinum neurotoxins

Non-proprietary name: BoNT type	OnabotulinumtoxinA	Abobotulinumtoxin A	Incobatulinumtoxin A	Pimabotulinumtoxin B
Company	Alergan, Inc., Irvine, CA, USA	Ipeen Biopharm Ltd., Wrexham, UK	Merz Pharmaceuticals GmbH, Frankfurt, Germany	Europe/US WorldMeds, Louisville, KY, USA
Trade name	Botox	Dysport	Xeomin	NeuroBioc/Myobioc
Machanism of action	Cleaves SNAP 25	Cleaves SNAP 25	Cleaves SNAP 25	Cleaves VAMP
Molecular weight, kD	900	500–900	150	700
Dosage form	Spray-dried powder	Freeze-dried powder	Freeze-dried power	Sterlie solution
Shef life, mo	36	24	36	24
Storage temperature, °C	<8	<8	<25	<8
pH value after reconstitution	7.4	7.4	7.4	5.6
Excipients	500 mg HSA and 0.9 mg NaCl in 100-U vial	125 mg HSA and 2.5 mg lactese in 500-U vial	1000 mg HSA and 4.7 mg sucrose in 100-U vial	0.5 mg/cc HSA; 0.01 M sodium succinate; 0.1 M NaCl; and SWI in 2500-U, 5000-U, and 10,000-U vials
Units per vial	50, 100, 200	300, 500	50, 100	2500; 5000; 10,000
Recommended volume of reconstitution	Maximum, 10 mL	Maximum, 1 mM	Maximum, 8 mL	0.5 mL; 1 mL; 2 mL
Total protein, ngivial	rv5	rv5	rv0.6	rv50
Antigenic protein load, ng/vial	rv0.8	Unknown	rv0.6	rv10.7
Biologic activity	100 MU-A/vial	500 MU-I/vial	100 MU-M/vial	1.0/2.5/10.0 kMU-E/vial
Specfic activity, Uing	20	40	167	75–125

From Ramirez-Castaneda. Movement Disorders, 2013. Reproduced by permission from publisher (Wiley)
BoNT botulinum toxin, *SNAP* soluble N-ethylmaleimide sensitive fusion protein (NSF) attachment protein, *VAMP* vesicle-associated membrane protien, *HSA* human serum albumin, *NaCl*, sodium chloride, *SWI* sterle water for injection, *MU-A* mouse units in the Alergen mouse lethality assay, *MU-I* mouse units in the Ipsen mouse lethality MU-M mouse units in the Merz mouse lethality assay, *kMu-E*, kilo-mouse unit equivalents.

muscle; it gets activated and reappears after the muscle paralysis caused by intramuscular BoNT injection.

Limited evidence in human suggests that larger volumes of the toxin may increase the diffusion of the toxin within injected and adjacent muscles. In one study, the effect of toxin volume was investigated in 10 human volunteers by injecting two different volumes of onaA (2 units/0.1 cc and 2 unit/0.02 cc) into the forehead muscles [19]. In 9 of the 10 patients, the side of the forehead which received the larger volume (and lower concentration) showed a more extensive diffusion effect. In a randomized, prospective study of 13 patients with spasticity [20], however, the investigators found no difference in efficacy between 50 and 100 units/cc dilutions of onaA preparations. In another double-blind, placebo-controlled study [21], comparing the effect of onaA and rimaB volume in 18 patients with hyperhidrosis, the increased volume of the toxin preparation increased the anhidrotic field for both toxins. The injection of rimaB, however, caused a larger anhidrotic area compared to an equal injected volume of onaA. Increasing injected volume of onaB also demonstrated more diffusion. The conversion ratio in this study was 1 onaA = 75 rimaB. Since the toxins are not truly interchangeable, different ratios have been used in clinical trials between onaA and onaB (from 1:40 to 1: 75); currently, 1:40 is an acceptable ratio [22], and one could argue that the higher dose of B toxin used in this study might have influenced the results. There is a need for larger controlled studies to discern the effect of volume and toxin type on diffusion of different BoNTs.

The effect of a single intramuscular injection versus multiple injections as a factor influencing the diffusion of BoNTs has not been thoroughly studied. Ramirez-Castenada et al. [13] state that multiple point injections along the length of affected muscle retain the biological effect of the toxin within the targeted muscle better than the single injections.

Immunology of BoNTs

The nontoxic protein complex (NAP) of BoNT structure is the main source of antigen formation after BoNT injection. The molecular structure and protein ratios within the nontoxic protein complex of BoNT have been described recently and consist of NBP (124 kDa), HC (90 kDa), LC (53 kDa), NAP-53 (50 kDa), NAP-33 (36 kDa), NAP-22 (24 kDa), and NAP-17 (17 kDa) [23]. Indirect ELISA analysis of BoNT/A and its associated proteins has shown that the BoNT/A protein complex antigen has a 32-fold higher titer than BoNT/A antigen itself, and most of this antigenicity is related to the NAP-33 protein component. In fact, activity of NAP-33 is equal to all the rest of the proteins in the NAP complex combined. The immune response to the botulinum neurotoxins is probably under genetic control, and the major histocompatibility of the host controls the appearance of blocking antibodies and emergence of immunoresistance [24].

The types of antibodies most associated with nonresponsiveness to BoNTs are neutralizing antibodies (nABs). This issue is particularly important when large doses of toxin may be needed such as for patients with severe spasticity or for some patients with advanced cervical dystonia (CD). Most studies of neutralizing antibodies in humans have been conducted with onabotulinumtoxinA (onaA) and in patients with CD. In regard to onaA, development of neutralizing antibodies (nABs) and loss of clinical response have been significantly reduced since the introduction of the new onaA formulation (1997), which contains only 5 ng (rather than 25 ng) of the old formulation in toxin's complex proteins. In one study [25], none of the 119 patients who had received the new onaA formulation developed neutralizing antibodies (nABs) compared to 9.5% among the 130 patients for whom the old formulation of toxin was used for treatment of cervical dystonia. In a prospective, open-label clinical trial, Brin et al. [26] investigated the development of nABs in 326 toxin-naïve patients who had an average of 9 injection sessions over a mean period of 2.5 years. All patients received the new formulation of onaA with a dose per session ranging from 148 to 213 units. Four of 326 subjects (2%) developed neutralizing antibodies against the toxin; three of these four (0.9% of 326) became eventually unresponsive to treatment which is documented by using the frontalis antibody test (FTAT). In another study [27], neutralizing antibodies to onaA were found in 32 of 191 patients (17%) with CD who had at least one to two injections of the old formulation of onaA (containing 25 ng of NAPs). These patients were then enrolled first in an open label and then in a double-blind, placebo-controlled clinical trial using the new toxin over a period of 2 years. One hundred and fourteen patients had antibody assessment both at the entry and at the exit time. Two of 114 patients (1.5%) developed new neutralizing antibodies; both patients, however, remained responsive to BoNT treatment during the course of the study.

These data indicate that with new formulation of onaA (used since 1997), only a small number of treated patients develop neutralizing antibodies and also a small number (less than 1%) manifest clinical unresponsiveness. As commented in a major recent review [1], botulinum neurotoxins, in general, seem to be poor antigens particularly when compared with their cousin molecule, the tetanus toxin. The relation of unresponsiveness to nAB titer and evolution of unresponsiveness over time is complex and deserves clarification through further investigations.

Regarding rimaB, an earlier communication based on data from a small number of patients with cervical dystonia (CD) had shown a high rate of nAB titers (in mouse assay) corresponding to unresponsiveness after 9 rimaB injection cycles in 44% of the studied population [28]. In a review paper [29], authors scrutinized the data of 4 large-scale RCTs conducted on rimaB efficacy in CD (1134 patients) in which nAB levels were provided. Authors found neutralizing antibodies in over 20% of patients, but there was no difference between nAB^+ and nAB− patients in regard to efficacy and continued responsiveness. They concluded that the presence

of neutralizing antibodies has no meaningful clinical significance in patients treated with rimaB. These issues suggest existence of major immunological differences between the two toxins, the importance of which deserves further exploration.

Chen and Dashtipour [30] summarized the relative immunogenicity of different BoNTs based on the total NAPs of each toxin:

> The total protein content (150 kD) toxin including nABs/ 100 units for ABO, INCO, ONA, and RIMA are 0.87, 0.44, 5, and 2.2 ng, respectively. Assuming that a dose equivalency ratio of INCO:ONA is 1:1, the total protein load with INCO (0.44 ng/100 units) would be at least 10-fold less than that of ONA (5 ng/100 units). If the dose equivalency ratio of ABO: ONA is 2:1–3:1, then the total protein load with ABO would be 2–3-fold less than that of ONA for each clinical dose. Thus, theoretically, INCO would carry a lower risk of immunogenicity, followed by ABO, ONA, and RIMA.

There is evidence that some cross-reactivity exists between type A and type B toxins. The first toxin could prime the immune response to stimulate the production of neutralizing antibodies to the second serotype faster than in a naïve individual devoid of antitoxin antibodies [31].

Overall, the above-mentioned data indicate low impact of immunogenicity in the current practice with all four commonly used FDA-approved BoNTs. Many factors influence the development of neutralizing antibodies and the clinical immune response; among these factors are the genetic makeup of the individual and prior exposures to toxins with similar homology, manufacturing process, toxin source, and perhaps the presence of denatured toxin acting as toxoid. Anatomic sites of injection may also be important in the development of immunogenicity, such as in the neck region, which is rich in lymph nodes [1]. Since immunogenicity increases with the dose of the toxin and frequency of administration, it is prudent to avoid excessive dosing and short intervals of application.

Most botulinum toxin clinics in the United States use a brief clinical test for defining unresponsiveness rather than measuring neutralizing antibodies through the cumbersome mouse immune-assay test. The most widely used clinical test is the frontalis antibody test (FTAT) in which the BoNT is injected at two points into frontalis muscle on one side (usually two 10 units for onaA). The injected side is then compared with the uninjected side in 10–14 days. If the BoNT is still effective, the frontalis muscle on the injected side flattens and contracts less compared to the uninjected side. Alternatively, one could use the response of the abductor digiti minimi (ADM) for this purpose. Injection of 15–20 units of onaA or other toxin in a comparable dose into ADM weakens this muscle sufficiently to limit abduction of the little finger. Finally, the response to toxin can be measured also electrophysiologically by recording the change in amplitude of compound muscle action potential (CMAP) in EMG which should show substantial reduction if the toxin is active. FTAT and ADM tests are easy to perform, and in complex cases, one could use both tests to ensure responsiveness to the injected BoNT.

Side Effects of BoNTs

The brochure of FDA-approved BoNTs carries a black box indicating a potential for serious side effects including major disability and even death. This is due to the fact that BoNT is one of the most potent natural toxins and when inappropriately used can be lethal. Absolute contraindications include hypersensitivity to BoNTs and presence of local infection. In practice and in experienced hands, however, BoNT therapy is generally safe, and most side effects are mild and transient. Pain at the site of injection, small local bleeding, and local infection may occur. Local injection of rimaB may cause more pain (compared to A toxins) due to the acidity of the solution; the pH of rimaB solution is 5.6 compared to the alkaline pH of BoNT-As (>7). Mild transient dysphagia after injection of the neck muscles in cervical dystonia occurs in 15% to 20% of patients which is often ignored by the patient and is not mentioned until asked. Chronic cough and upper respiratory tract infection rarely develops with deep neck injections.

Acute hypersensitivity reaction to BoNTs is extremely rare. Theoretically, presence of human albumin in the toxin carries a small risk of slow virus disease. No such case has ever been documented with BoNT treatment over three decades and including millions of patients. Patients with neuromuscular disorders are at risk of deterioration and increased severity of symptoms. BoNT treatment is not recommended in patients with myasthenia gravis or patients taking drugs which are known to significantly impair neuromuscular transmission (e.g., aminoglycosides, neuromuscular blockers). BoNT therapy is also currently not recommended in pregnancy due to the paucity of information in this area. Several new studies, however, have shown that BoNT treatment of pregnant women is safe probably due to low systemic absorption of the toxin and very low toxin transfer through the placenta [32, 33].

In a large multicenter study that included 214 patients, the side effects of onabotulinumtoxinA injection at a mean dose of 241.3 units (range, 95–360 units) were compared with the placebo (saline) [27]. The screened side effects included neck pain, back pain, dysphagia, rhinitis, headache, hypertonia, increased pain, flu symptoms, increased cough, muscle weakness, and sinus infection. Only incidence of rhinitis was significantly higher in the toxin group ($P < 0.05$).

In my nearly 30 years of experience with BoNT therapy, more than half of which included two full days per week of injecting a large number of patients, I have never witnessed a serious side effect requiring hospitalization. Among thousands of injections for cervical dystonia, I had two patients with moderate dysphagia that required close watch for several weeks; both fully recovered. In both cases, there was bilateral injection of anterior neck muscles, and the total dose exceeded 300 units. Despite my positive experience, which is shared by many others, one should not lose sight of the fact that botulinum neurotoxin is one of the most potent toxins in nature. Therefore, clinicians who are engaged in this practice should always pay close attention to proper dosing and dilution. In the case of muscular injection, familiarity with muscle anatomy is essential to avoid injecting the wrong muscles.

Serious side effects should be referred to emergency department immediately and dealt with aggressively since time is essential. Fortunately, with the availability of modern intensive care units, most intoxicated patients when detected early survive with proper and maintained support of respiration.

In the area of pain treatment, which is the subject of this book, logically the patients should experience less side effects than patients with spasticity or dystonia due to a lower dose of the used toxin. Also, injections are usually subcutaneous or intradermal with a lower potential of spreading to vital structures. The literature on BoNT therapy in chronic migraine and studies published on several human pain disorders supports lower incidence of side effects with BoNT treatment in pain disorders (Chaps. 4 to 19 of this book).

References

1. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: biology, pharmacology, and toxicology. Pharmacol Rev 2017 ;69(2):200–235. https://doi.org/10.1124/pr.116.012658. PMID: 28356439; PMCID: PMC5394922.
2. Atassi MZ. Basic immunological aspects of botulinum toxin therapy. Mov Disord. 2004;19(Suppl 8):S68–84.
3. Hanna E, Pon K. Updates on botulinum neurotoxins in dermatology. Am J Clin Dermatol 2020;21(2):157–162. https://doi.org/10.1007/s40257-019-00482-2. PMID: 31782076.
4. Pickett A. Dysport: pharmacological properties and factors that influence toxin action. Toxicon. 2009;54:683–9.
5. Simpson L. The life history of a botulinum toxin molecule. Toxicon. 2013;68:40–59.
6. Swaminathan S. Molecular structures and functional relationships in clostridial neurotoxins. FEBS J. 2011;278:4467–85.
7. Dong M, Masuyer G, Stenmark P. Botulinum and Tetanus Neurotoxins. Annu Rev Biochem 2019 88;811–837. https://doi.org/10.1146/annurev-biochem-013118-111654. . Epub 2018 Nov 2. PMID: 30388027; PMCID: PMC7539302.
8. Choudhury S, Baker MR, Chatterjee S, Kumar H. Botulinum toxin: an update on pharmacology and newer products in development. Toxins (Basel) 2021;13(1):58. https://doi.org/10.3390/toxins13010058. PMID: 33466571; PMCID: PMC7828686 .
9. Pirazzini M, Azarnia Tehran D, Leka O, Zanetti G, Rossetto O, Montecucco C. On the translocation of botulinum and tetanus neurotoxins across the membrane of acidic intracellular compartments. Biochim Biophys Acta 2016;1858(3):467–474. https://doi.org/10.1016/j.bbamem.2015.08.014. Epub 2015 Aug 22. PMID: 26307528.
10. Hallett M. Explanation of timing of botulinum neurotoxin effects, onset and duration, and clinical ways of influencing them. Toxicon 2015;107(Pt A):64–67. https://doi.org/10.1016/j.toxicon.2015.07.013. Epub 2015 Jul 26. PMID: 26220801; PMCID: PMC4658210.
11. Dashtipour K, Wietek S, Rubin B, Maisonobe P, Bahroo L, Trosch R. AbobotulinumtoxinA using 2-mL dilution (500 U/2-mL) maintains durable improvement across multiple treatment cycles. J Clin Mov Disord 2020 ;7:8. https://doi.org/10.1186/s40734-020-00090-x. PMID: 32884828; PMCID: PMC7457764.
12. Liu A, Carruthers A, Cohen JL, et al. Recommendations and current practices for the reconstitution and storage of botulinum toxin type A. J Am Acad Dermatol. 2012;67:373–8.
13. Ramirez-Castaneda J, Jankovic J, Comella C, Dashtipour K, Fernandez HH, Mari Z. Diffusion, spread, and migration of botulinum toxin. Mov Disord. 2013;28:1775–83.

14. Lange DJ, Rubin M, Greene PE, et al. Distant effects of locally injected botulinum toxin: a double-blind study of single fiber EMG changes. Muscle Nerve. 1991;14:672–5.
15. Garner CG, Straube A, Witt TN, Gasser T, Oertel WH. Time course of distant effects of local injections of botulinum toxin. Mov Disord. 1993;8:33–7.
16. Punga AR, Eriksson A, Alimohammadi M. Regional diffusion of botulinum toxin in facial muscles: a randomised double-blind study and a consideration for clinical studies with split-face design. Acta Derm Venereol 2015;95(8):948–951. https://doi.org/10.2340/00015555-2093. PMID: 25766591.
17. Borodic GE, Ferrante R, Pearce LB, Smith K. Histologic assessment of dose-related diffusion and muscle fiber response after therapeutic botulinum A toxin injections. Mov Disord. 1994;9:31–9.
18. Carli L, Montecucco C, Rossetto O. Assay of diffusion of different botulinum neurotoxin type a formulations injected in the mouse leg. Muscle Nerve. 2009;40:374–80.
19. Hsu TS, Dover JS, Arndt KA. Effect of volume and concentration on the diffusion of botulinum exotoxin A. Arch Dermatol. 2004;140:1351–4.
20. Francisco GE, Boake C, Vaughn A. Botulinum toxin in upper limb spasticity after acquired brain injury: a randomized trial comparing dilution techniques. Am J Phys Med Rehabil. 2002;81:355–63.
21. Kranz G, Paul A, Voller B, et al. Long-term efficacy and respective potencies of botulinum toxin A and B: a randomized, double-blind study. Br J Dermatol. 2011;164:176–81.
22. Dressler D, Eleopra R. Clinical use of nonA botulinum toxins. Botulinum toxinB Neurotox Res. 2006;9:121–5.
23. Bryant AM, Cai S, Singh BR. Comparative immunochemical characteristics of botulinum neurotoxin type A and its associated proteins. Toxicon. 2013;72:126–32.
24. Atassi MZ. Basic immunological aspects of botulinum toxin therapy. Mov Disord 2004;19 Suppl 8:S68–S84. https://doi.org/10.1002/mds.20020. PMID: 15027058.
25. Jankovic J, Ahsan J, Vuong KD. Comparison of immunogenicity of old versus current BTOX in cervical dystonia. Naunyn Schmiedeberg's Arch Parmacol. 2002;365(Suppl. 2):65.
26. 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.
27. Charles D, Brashear A, Hauser RA, Li HI, Boo LM, Brin MF. CD 140 Study Group. Efficacy, tolerability, and immunogenicity of onabotulinumtoxina in a randomized,double-blind, placebo-controlled trial for cervical dystonia. Clin Neuropharmacol. 2012;35:208–14.
28. Dressler D, Eleopra R. Clinical use of non-A botulinum toxins: botulinum toxin type B. Neurotox Res. 2006;9:121–5.
29. Chinnapongse RB, Lew MF, Ferreira JJ, Gullo KL, Nemeth PR, Zhang Y. Immunogenicity and long-term efficacy of botulinum toxin type B in the treatment of cervical dystonia: report of 4 prospective, multicenter trials. Immunogenicity and long-term efficacy of botulinum toxin type B in the treatment of cervical dystonia: report of 4 prospective, multicenter trials. Clin Neuropharmacol. 2012;35:215–23.
30. Chen JJ, Dashtipour K. Abo-,inco-,ona-,and rima-botulinum toxins in clinical therapy: a primer. Pharmacotherapy. 2013;33:304–18.
31. Aoki KR. Pharmacology and immunology of botulinum toxin serotypes. J Neurol. 2001;248(Suppl 1):3–10.
32. Wong HT, Khalil M, Ahmed F. OnabotulinumtoxinA for chronic migraine during pregnancy: a real world experience on 45 patients. J Headache Pain 2020;21(1):129. https://doi.org/10.1186/s10194-020-01196-1. PMID: 33121432; PMCID: PMC7599093.
33. Li W, Tang M. Application of botulinum toxin in pregnancy and its impact on female reproductive health. Expert Opin Drug Saf 2020;19(1):83–91. https://doi.org/10.1080/14740338.2020.1707803. Epub 2019 Dec 26. PMID: 31868020.

Chapter 3
Analgesic Effects of Botulinum Neurotoxins: Data from Animal Studies Volunteers

Introduction

Over the past 20 years, a large volume of literature has been published in the field of pain based on investigations conducted on animals and asymptomatic human volunteers. These data have defined new pain receptors, expanded our knowledge on pain mediators/modulators, and refined our understanding of pain pathophysiology. Moreover, new data derived from experiments on animals and human volunteers have provided important information on how BoNTs influence pain mechanisms and alleviate pain by altering and modifying the function of nerve endings, 0-), and spinal and brain stem neurons. In this chapter, the pathophysiology of pain based on this novel data is presented and discussed.

Pathophysiology of Pain at Peripheral and Central Levels

Pain is an unpleasant and annoying sensation which is usually provoked by a noxious stimulus contacting skin, bone, or muscles; a less common form of pain, central pain originates from the disturbance of structures mostly at the level of spinal cord or thalamus. Specialized structures and pathways of the somatosensory system participate in conveying the pain signals to the sensory cortex (Fig. 3.1). Final perception of pain at the cortical level requires four sequential processes: transduction, transmission, modulation, and perception. During the transduction phase, noncapsular, nociceptive nerve endings are stimulated by pain-inducing agents (heat, cold, chemical, and mechanical). Stimulation of free nerve endings by noxious stimuli opens sodium channels which are present on the sensory nerves in abundance. With sodium influx, the negative charge inside of the cell (−70 uV) moves toward positivity, and when it reaches +40, it generates an action potential that travels along

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_3

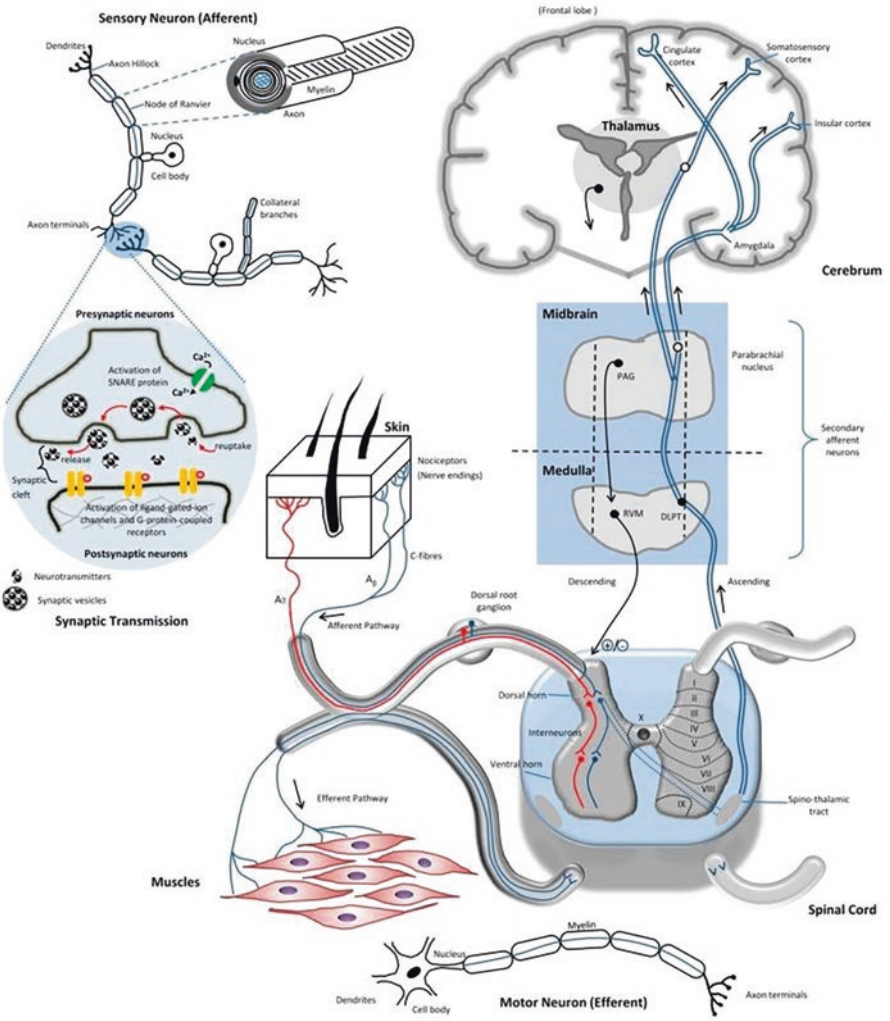

Fig. 3.1 Pain pathways. (From Yam et al. Int J mol Sci. Reproduced under Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/). Publisher MPDI)

sensory pain axons conveying nociceptive information to dorsal root ganglion (DRG) and to the central nervous system. The sensory fibers that convey pain signals are unmyelinated C and small, myelinated Aδ fibers. C fibers are very thin with a diameter of less than 2 micrometers and a conduction velocity of about 2–5 meters/second. They are activated by poorly localized stimuli and are polymodal, that is, they respond to a variety of stimuli, such as chemical agents, heat, and cold. Aδ fibers are the smallest myelinated fibers with a diameter of 2–5 μm and with faster conduction of 30 meters/second compared to C fibers [1]; they respond to tactile and temperature stimulation.

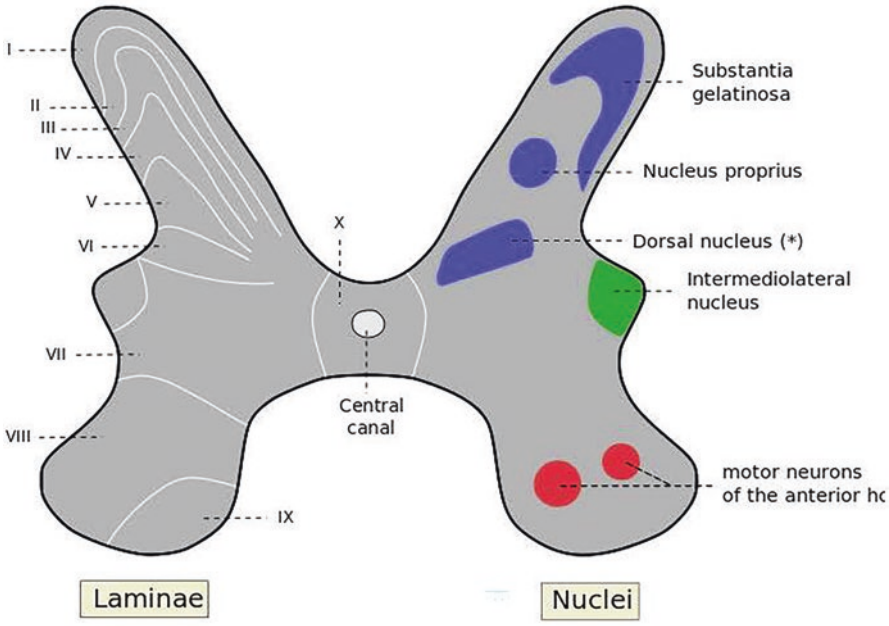

Fig. 3.2 Anatomical location of Rexed lamina including substantia gelatinosa (lamina II)

The C fibers are peptidergic or nonpeptidergic. The peptidergic fibers use Substance P (SP) and calcitonin gene-related peptide (CGRP) as pain signal transmitters. The second nociceptive neurons are located in the gray matter of the posterior horn of the spinal cord which has a laminar structure (Rexed lamina), numbered from layers I to VII (Fig. 3.2). The peptidergic C fibers end in Rexed lamina I and outer part of Rexed lamina II (substantia gelatinosa) which are the superficial layers of the spinal dorsal horn, whereas nonpeptidergic fibers terminate in the inner part of lamina II [2].

Dorsal root ganglia (DRG), which are located in dorsal roots, contain thousands of specialized, bipolar sensory cells that encode and transmit sensory information (received from periphery) to the spinal cord sensory neurons. Peptidergic neurons of DRG contain substance P (SP), CGRP, and somatostatin. The most common neurotransmitter made by DRG cells is glutamate, but many cells also express SP, a major nociceptive transmitter [3]. After injury, C fibers may alter DRG sensitivity by changing the intracellular calcium level affecting N-methyl-aspartate receptors of DRG neurons. The resultant plastic reorganization of DRG is believed to play an important role in the development of peripheral sensitization and process of pain chronicity [4].

The C and Aδ fibers enter the spinal cord via posterior roots and, after traveling a few segments in the spinothalamic tract, synapse with ipsilateral sensory neurons (mainly in Rexed areas I and II). The axons of these neurons then cross the spinal

gray matter in the anterior decussation and travel in the contralateral spinothalamic tract rostrally (Fig. 3.1).

At the spinal cord level, lamina I carries both nociceptive and wide dynamic range neurons. The nociceptive neurons of this lamina express a variety of peptide transmitters such as SP, CGRP, serotonin, and enkephalin and respond to noxious stimuli. Lamina II is rich in inhibitory interneurons that release GABA [4]. These neurons arborize to the other lamina of the posterior horn including lamina I and II. It is believed that the neurons of lamina II (substantia gelatinosa) have a modulatory effect on incoming pain signals [5].

In the thalamus, the posterior–inferior segment of ventralis posterior (VP) nucleus is a major site of transmission of the nociceptive signals to the cortex; this region is the main target of deep brain stimulation (DBS) for relieving intractable pain [6]. The central nuclei of the thalamus (intralaminar, central medial, and parafasciculus) also receive nociceptive input from the spinothalamic tract as well as input from the brainstem reticular formation.

At the cortical level, primary and secondary somatosensory cortices (SI and SII) are the main recipients of the nociceptive information (Fig. 3.1). SI, due to its graded and proportional response to pain signals, is considered to be the main site for the appreciation of the discriminative quality of pain. SII receives nociceptive information from both contralateral and ipsilateral spinothalamic tracts. Nociceptive signals end primarily on cortical levels III and IV. Other cortical areas which receive pain signals include the insular, dorsolateral, prefrontal, and cingular cortices as well as the amygdala. The anterior cingular cortex which receives information from intralaminar nuclei of the thalamus is believed to be involved in motivational and emotional responses to pain [7].

Pain Modulation

The traveling pain signals to the cortex are modulated both on the way to the cortex and by specific descending tracts which influence spinal sensory neurons. One purpose of this pain modulation is protecting the cortex from excessive nociceptive stimuli. As already mentioned, on the ascending arm of the pain system, substantia gelatinosa at the spinal level and central nuclei of the thalamus, which receive input from the reticular formation, are all involved in pain modulation. A descending and better-studied system for pain modulation exists that includes neurons of periaqueductal gray region in the midbrain as well as the neurons of rostroventromedial (RVM) medulla which are a part of the medullary reticular formation. These neurons exert their antinociceptive effects on sensory neurons of lamina I and II of dorsal horn using noradrenalin and serotonin as neurotransmitters.

In addition, the descending endogenous opioid pain-modulating system also reduces pain transmission. Activation of mu-opioid receptors blocks pain both centrally and via activating abovementioned descending modulating systems. It does this through changing membrane conductivity and the state of protein

phosphorylation. Dynorphin, an opioid peptide, is present in periaqueductal gray (PAG), midbrain reticular formation, and the laminae I to IV of spinal dorsal horn [4, 8].

Data from Animal Studies

Data from animal studies indicate that BoNTs can reduce or block pain transmission in peripheral nerves and at the level of DRG, spinal cord, and midbrain. Convincing data for the thalamic and cortical levels are not available, however. BoNTs block pain transmission through influencing the function of a variety of pain receptors, pain transmitters, and modulators such as substance P and CGRP as well as opioid receptors.

One of the first studies investigating the analgesic effect of BoNTs was published by Cui and coworkers in 2004 [9]. The authors used the formalin pain model for their experiments. In this model, subcutaneous injection of formalin in rat's paw produces a biphasic pain response. The first peak of pain that develops within 5 min of injection is caused by the direct chemical effect of formalin upon C fibers. The second peak occurs within 15–60 min of injection and is a more intense pain induced by local tissue inflammation [10] during which there is local accumulation of inflammatory agents (neuropeptides, kinins) and pain mediators (glutamate, substance P, and CGRP) at the injection site. It is believed that, unlike the first peak, the second peak of pain is not related to the irritation of C fibers, but rather it represents pain related to central sensitization of the pain pathways. Cui et al. pretreated rats with onaA for 2–12 days in order to observe the timeframe of onaA's effect on formalin-induced pain. Four groups of rats that received 3.5, 7, 15, and 30 μ/kg of onaA diluted in 0.9% saline (22 ml bolus) into the hind paw subcutaneously. For control rats, the same volume of 0.9% saline was injected into the hind paw. The rats were then injected with 50 ml of 5% formalin in the same paw, and their pain behavior (lifting/licking) was recorded within 5 minutes post injection and, again, at 15–30 min post injection corresponding to the first and second peaks of formalin-induced pain. Pretreatment with onaA (at doses mentioned above) 5 days prior to formalin injection significantly reduced the level of formalin-induced pain in a dose-dependent manner (Fig. 3.3).

As evident in Fig. 3.3, the second peak of pain (inflammatory peak) was the one most affected by the onaA pretreatment. The largest dose (30 units/kg) used in this experiment affected both peaks, but rendered the animals too lethargic to make a reliable assessment. The authors also noticed significant reduction in paw edema in onaA-treated animals. Furthermore, the animals pretreated with onaA demonstrated significant reduction of accumulated tissue glutamate (after formalin injection) compared to animals who received saline only; the mean tissue glutamate level was 280.2 ng/ml for those injected with saline versus a mean of 208.4 ng/ml for those treated with 15 μ/kg of toxin ($P < 0.05$). These results demonstrated that

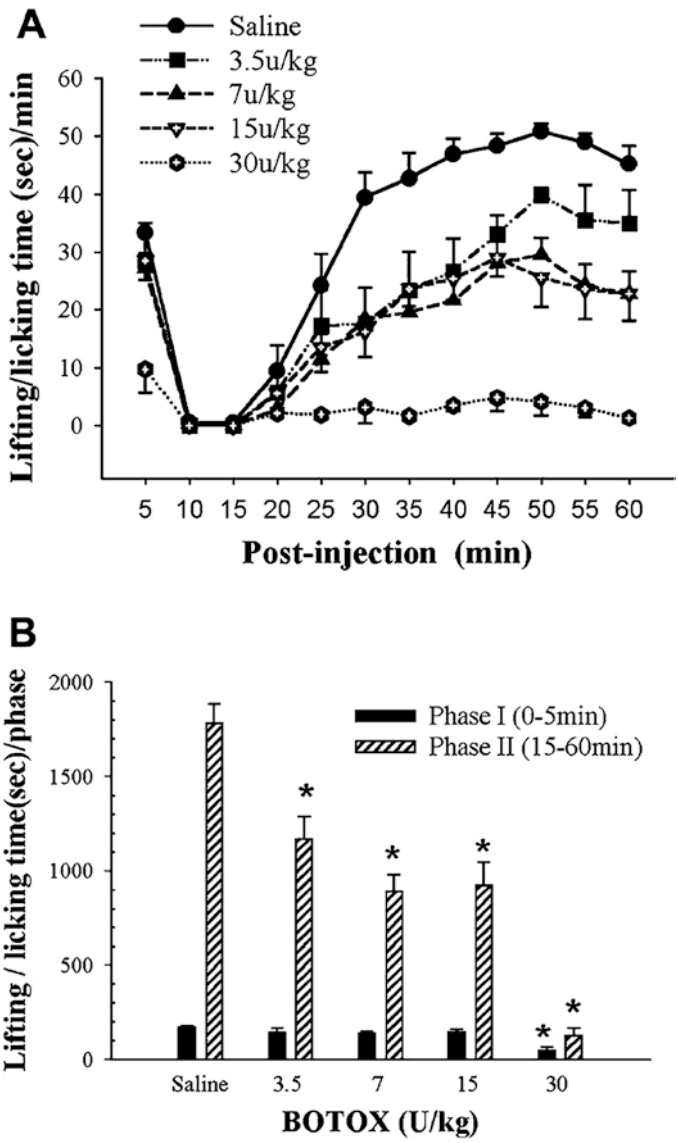

Fig. 3.3 Pretreatment with BoNT-A reduces formalin injection-induced paw pain in rats in a dose-dependent manner. (Cui et al. [9], with permission from the journal *Pain* and publisher)

onabotulinumtoxinA exerts both analgesic and anti-inflammatory effects in formalin-induced model of pain.

Ten years later, Marino et al. [11], in a similar experiment, investigated the effect of botulinum toxin-B (rimabotulinumtoxinB, rimaB/Myobloc) in formalin pain model. One unit of BoNT-B or a similar volume of saline was injected into

intraplantar region unilaterally in mice. Pretreatment of mice with BoNT-B before saline injection reduced intraplantar formalin-evoked flinching, capsaicin-evoked plasma extravasation in the hind paw, formalin-evoked dorsal horn substance P (SP) release, formalin-evoked dorsal horn neuronal activation (c-fos) as well as ipsilateral dorsal root ganglion (DRG) vesicle-associated membrane protein (VAMP) and ipsilateral SP release otherwise evoked bilaterally by intrathecal capsaicin administration. This study showed that injection of BoNT-B affected and reduced the release of SP both by DRG neurons and by spinal cord sensory neurons of the dorsal horn.

In another experiment, Welch et al. [12] studied the effect of botulinum toxins A, B, C, and F on SP release from DRG neurons that had been exposed to elevated extracellular potassium in order to enhance their calcium-dependent SP release. All toxins exerted some degree of SP release inhibition, but this effect was most prominent for BoNT-A and least notable for BoNT-B. BoNT-A cleaved the SNAP 25 within 2 h, but inhibited SP release at 4th hour. In another study [13], researchers demonstrated that acute bladder injury after exposure to HCL resulted in marked release of SP and CGRP into the injured bladder tissue (1235 and 1655 pg/g, respectively, compared to 183 and 449 pg/g for controls, respectively) ($P < 0.001$). The levels of SP and CGRP dropped to 870 and 1033 pg/g, respectively, following BoNT-A injection ($P < 0.05$ and <0.01). Similar results with BoNT-A administration were observed on elevated levels of SP and CGRP after chronic exposure to cyclophosphamide.

In trigeminal neurons, the release of CGRP was blocked after exposure to BoNT-A [14]. In these neurons, SNAP25 and CGRP were noted to be colocalized. A, C, and D botulinum toxins (but not B) also blocked calcium-dependent SP release from the same neurons [14]. BoNTs, however, failed to block capsaicin-induced elevation of CGRP from trigeminal neurons. In a later experiment, the same group of researchers studied and noted that an A/E chimera of BoNT which specifically targets the sensory cells can subdue capsaicin activation of TRPV1 nociceptive channel as well as the rise of CGRP that results from capsaicin exposure [15].

Matak et al. [16] demonstrated the role of SP in the analgesic effect of BoNT-A by studying knockout mice lacking encodement of SP-neurokinin gene. In this model, injection of BoNT-A before formalin in mice showed no analgesic effect. In another study [17], investigators found that injection of botulinum toxin-A reduced the number of immunoreactive substance P (SP-IR) and calcitonin gene reactive protein (CGRP) in the sensory neurons of dorsal root ganglia innervating pig's bladder. In a recent experiment, special delivery of a genetically engineered BoNT-D protease (light chain) to the sensory cells prevented release of substance P from sensory neurons [18]. Further support for effect of BoNTs on CGPR release was provided in another recent study where authors delivered the light chain (active moiety) of several BoNTs to rat's DRG cells using engineered herpes simplex virus as a vector. They noted a marked decrease in CGRP release from DRG cells; this effect was most noticeable for Type D and A toxins.

Effect of Botulinum Toxins on Pain Channels and Receptors

Effect on Sodium Channels

As mentioned above, activation of Na + channels in response to a noxious stimulus generates a propagating action potential in the peripheral nerve. Sodium channels are present in abundance on pain receptors, C fibers, and DRG, and hence play a pivotal role in transmitting nociceptive signals. Among a variety of known Na + channels, Na1.7, Na1.8, and Na1.9 are most relevant to pain. The Na + channels are classified as tetrodotoxin sensitive (TTX-S) with a fast activation/inactivation nature, whereas tetrodotoxin-resistant (TTX-R) channels have slow activation/inactivation. Na1.7 is a TTX-S channel, whereas Na 1.8 and 1.9 are TTX-R type of sodium channels. Sodium channel mutations are associated with some of the most severe forms of human pain such as the pain experienced in erythromelalgia [19]. Shin et al. [20] have shown that injection of botulinum neurotoxin A2 significantly inhibits neuronal Na channel in rats. Unlike tetrodotoxin (TTX), local anesthetics, and antiepileptic drugs, BoNT completely inhibited Na channels in a concentration-dependent manner. The authors concluded that type A neurotoxins inhibit membrane Na (+) channel activity in CNS neurons and also in both TTX-sensitive and -insensitive peripheral dorsal ganglion cells (40% more than controls). Based on their results, they suggested that BoNT-A2 has a potential for treatment of epilepsy and several types of pain.

Effect on Transient Receptor Potentials (TRP) Channels

One of the major areas of progress in understanding the molecular physiology of pain is the discovery of transient receptor potential channels (TRPs) [21]. TRPs are expressed specifically on sensory nociceptive neurons. These receptors which are made of vanilloid protein (TRPV) are cation-gated calcium channels. Produced by DRG neurons, these protein channels are then transferred by axonal transport peripherally to the nerve endings and centrally to dorsal horn neurons (Rexed lamina II-substantia gelatinosa). There are several types of TRP channels designated as TRP1, TRP2, TRP3, TRP4, and TRP8, but TRPV1 plays the dominant role in neuropathic and nociceptive pain. The influx of cations, especially calcium, opens the TRPV1 channel leading to hyperexcitability of the peripheral and central neurons enhancing pain. Heat of over 42 °C, chemicals such as capsaicin, and low pH of <5.9 directly stimulate and open the TRPV1 channel. A large number of other agents also activate TRPV1 indirectly including inflammatory mediators such as prostaglandin E2, proteases, and nerve growth factor (NGF) [22]. The function of TRPV1 channel seems to be different in peripheral (DRG) and central (dorsal horn of spinal cord) neurons. While TRPV1 in DRG neurons receives pain signals from periphery and conducts the information to spinal cord sensory neurons, activation of

TRPV1 in spinal cord neurons releases glutamate locally and promotes central excitability of the sensory neurons [23].

Inflammatory hyperalgesia is absent in TRPV1 knockout mouse [24], and TRPV1 expression is markedly enhanced in neuropathic pain and inflammatory hyperalgesia. Intrathecal injection of TRPV1 antagonist AS1928370 alleviates the neuropathic pain in the mouse model [25]. Another TRPV channel, TRPA1, is also upregulated in DRG and dorsal horn neurons by peripheral inflammation and is implicated in cold hyperalgesia caused by inflammation and nerve injury [26].

Several studies have shown that BoNTs can reduce or block the activity of TRP channels. In one study, injection of an engineered A/E botulinum toxin chimera reduced the function of TRP1 channel and improved capsaicin-induced hyperalgesia [15]. Xiao et al. [27] demonstrated that rats with neuropathic pain, when injected with botulinum toxin type A, showed reduction of clinical hyperalgesia and TRPV1 expression after BoNT exposure. Subcutaneous BoNT-A injection (0.25, 0.5, or 5 ng/kg) into the face close to the ophthalmic division of the trigeminal ganglion neurons decreased TRPV1-immunoreactive neurons in the trigeminal ganglion and TRPV1-immunoreactive fibers in rat trigeminal nerve terminals [28]. The authors believed that the mechanism by which BoNT-A reduced TRPV1 expression was inhibition of TRPV1 plasma membrane trafficking and proteasome-mediated degradation in the cytoplasm. Further information on the effect BoNTs on TRP channels comes from the recent works of Zhang et al. [29] and Nuget et al. [30]. The former authors studied the effect of subcutaneous facial injection of BoNT-A on TRP4 expression in rat's trigeminal neuralgia induced by chronic constriction injury to the infraorbital nerve. Four days after BoNT-A injection, rats injected with 3 and 10 units of BoNT-A demonstrated significantly higher pain threshold compared to control rats who had not received toxin injections. Additionally, rats injected with this toxin showed significant reduction of expression of TRP4 compared to controls ($P < 0.5$). Nuget et al. [30] have also observed decreased expression of TRP1 in neonatal rats' dorsal root ganglion using an E/A neurotoxin chimera in their experiment; EA is an engineered toxin linking C chain of E to full chains of A toxin.

Effect on Purinergic Channels

Purinergic receptors are ligand-gated Ca++ channels that respond to adenosine triphosphate (ATP) stimulation. The P2x3-ATP-responsive receptor channel is specifically expressed in sensory nociceptive neurons. Purinergic channels have both chemical and mechanical sensitivity. ATP applied to a blister base causes pain in humans and also induces pain behavior in animals [31].

Apostolidis et al. [32] studied immunoreactivity of P2X3 and TRPV1 channels in the bladder biopsies of 38 patients with bladder overactivity (22 neurogenic type) after intravesical BoNT-A injection. Immunoreactivity of both channels was significantly decreased at 4 and 16 weeks after BoNT injection; this finding was associated with improvement of the patients' urinary urgency. Xiao et al. [33] assessed the

effects of BoNT-A or saline injection on P2X3 receptors in DRG neurons of rats experiencing neuropathic pain after L5 ventral root transection. Subcutaneous injection of BoNT-A into the rat's left hind paw significantly reduced expression of P2X3 and pain behavior on days 4, 8, and 16 after surgery. Liu et al. [34], retrospectively, evaluated the results of intravesical BoNT-A injection (200 units) in 27 patients with overactive bladder (OAB) both clinically (6 patients) and in regard to its effect on tissue P2X3. BoNT-A injection cleaved SNAP 25 and effectively decreased the frequency of urgency episodes in patients with OAB. Liposome-encapsulated BoNT-A injections decreased urothelial P2X3 expression in the five responders ($p = 0.04$). These data suggest that purinergic P2X3, like TRPV receptor, plays an important role in nociception, and reducing the function of P2X3 receptor has a potential to alleviate pain.

The Role of Nerve Growth Factor (NGF) in Pain

Emerging data in the literature indicate that nerve growth factor is a major factor in nociception [31]. Development of peripheral nerve endings, C fibers, DRG neurons, and nociceptive sensory spinal neurons is highly dependent on NGF. A specific NGF receptor, Tyrosine receptor kinase A (TrkA), is expressed in abundance on nociceptive neurons. Long-term exposure to NGF increases production of SP and CGRP as well as expression of Na+, P2X3, and TRPV1 channels [35]. NGF antagonists have been shown to exert analgesic effects [36]. In human, botulinum toxin injection into the overactive bladder has been shown to reduce the level of urinary NGF levels [36], but the effects of BoNT on NGF have not been properly studied yet in animal pain models.

The Effects of Botulinum Toxins on Inflammation

As stated earlier in this chapter, exposure to chemicals, high or low temperature, and following nerve injury, pain mediators such as glutamate accumulate locally in the injured tissue [9, 11]. This would lead to vasodilation and development of inflammation in the injured area. Inflammation, which is usually associated with lower tissue pH, starts a cascade of events leading to enhancement of pain through influencing the function of pain receptors via a variety of mechanisms. Inflammatory cells can activate local production of NGF which enhances pain (see above). It has been shown that in acute inflammation, macrophages can directly invade DRG neurons and interrupt the function of DRG's sensory neurons [37]. Low pH caused by inflammation also triggers the acid-sensing sodium channels, resulting in hyperexcitability of the neural tissue. Furthermore, lowered tissue pH activates ATP

production, which in turn opens the purinergic channels and TRPV1 channels leading to more excitation of nerve terminals. The resultant effects are mechanical hyperalgesia and thermal hyperalgesia due to stimulation of dermal nociceptors along with heightened and sustained excitability of nociceptive nerve terminals (peripheral sensitization) [38].

The literature pertaining to the presence of local inflammation in the peripheral nervous system, as observed in experimental pain models, is controversial. While some studies have shown clear evidence of local inflammation at the site of peripheral pain, others have failed to do so. Three controlled studies have demonstrated that local injection of BoNTs reduces accumulation of glutamate and local edema caused by local injection of pain-inducing agents [9, 11, 39]. Two of these studies injected BoNT-A and -B before formalin injection into rat's paw [9, 11]. One study was performed in asymptomatic human volunteers in whom increased tissue glutamate release was measured by dermal microdialysis [39].

In contrast to above-mentioned studies, Attal and coworkers did not find increased tissue accumulation of SP and CGRP in biopsy specimens of patients with neuropathic pain [40]; however, the normal values used in their laboratory were not provided. Furthermore, in a study of capsaicin- and carrageenan-induced neuropathic pain (injected intratarsally), investigators did not find that pretreatment with BoNTs reduces focal edema or protein extravasation caused by these two agents [41].

Despite this controversial data reported on the presence of inflammation in experimental pain models (which may be related to the type of pain model and to technical issues), substantial literature indicates that BoNTs exert their antinociceptive effect through subduing inflammatory processes; they do so by both affecting production and release of inflammatory agents and also by affecting major cellular players such as microglia in the inflammatory cascade.

Intra-articular injection of Botulinum toxin-A reduces expression of proinflammatory cytokines in the synovial tissue as well as reducing cartilage degeneration and local infiltration of inflammatory cells [42]. In a study using Freund adjuvant (FA) to inflame and destroy a joint, authors demonstrated that intra-articular injection of BoNT-A before FA injection reduces the number of inflammatory cells around the articular cartilage and synovial membrane of the involved joint [43]. In cyclophosphamide-induced cystitis, intravesical injection of BoNT-A decreased inflammatory cell accumulation and levels of SP and CGRP as well of bladder sensitivity and pain behavior [44]. In animal model of capsaicin-induced prostatitis, injection of BoNT-A into bladder wall decreased inflammatory cells and the expression of cyclooxygenase 2 (COX2) in the bladder and spinal cord [45]. BoNT-A inhibits a family of G proteins including Rho guanosine triphosphatase which is essential for activation of interleukin-1, an important proinflammatory cytokine [46]. Intraprostatic injection of BoNT type A inhibits cyclo-oxygenase-2 expression and suppresses capsaicin-induced prostatitis in animal models [47].

In a rat constrictive injury model, injection of BoNT-A into metatarsal joint alleviated the neurogenic pain. The pain relief was associated with suppression of

inflammatory cytokine release from microglia; it was attributed to targeting and cleavage of a newly discovered SNARE protein, SNAP23 [48]. In another animal study of Freund's adjuvant-induced arthritis, intra-articular injection of BoNT-A reduced pain and subdued the release of inflammatory agents released by activated spinal cord microglia [49]. Injection of BoNT-A into temporomandibular joint of rats affected by antigen (Freund's adjuvant) alleviated joint pain and subdued the microglial P2X7 pain pathway activated by this antigen [50]. In the sciatic nerve injury model, intraplantar injection of BoNT-A activated microglia in the lumbar spinal cord ipsilateral to the injury along with improvement of thermal and mechanical hypersensitivity [51]. In another study, using the same technique of injection and same toxin, examination of the spinal cord demonstrated activation of microglia and astrocytes in dorsal and ventral cords [52]. In another study, injection of BoNT-A into the paw of the rats with pain related to sciatic nerve injury alleviated pain behavior, decreased the level of pro-inflammatory cytokines, increased the level of anti-inflammatory interleukins, and decreased the activity of microglia in DRG and spinal cord [53].

Spinal Cord Gabaergic Neurons and Pain: Effects of Botulinum Toxins

The activity of both superficial and deep laminae of the spinal cord's dorsal horn is controlled by two inhibitory neurotransmitters, gamma-aminobutyric acid (GABA) and glycine. The interneurons of dorsal horn and inhibitory descending fibers act on GABA-A (ionotropic) and GABA-B (metatropic) receptors; activation of these receptors reduces excitation of spinal sensory neurons via hyperpolarization of the postsynaptic membrane and/or activation of a shunting conductance. Additionally, GABA can directly decrease glutamate release from primary sensory afferent fibers [54]. Therefore, enhanced function of Gabaergic neurons can reduce central sensitization which results from hyperexcitability of spinal cord sensory neurons in chronic pain disorders.

Drinovac et al. [55] studied the role of the Gabaergic system on the analgesic effect of BoNT-A in the formalin model of inflammatory pain and in mechanical allodynia. In their experiment, intrathecal (1 ug) or intraperiteoneal 0.6–0.8 mg injection of bicuculline (GABA-A antagonist) prevented antinociceptive effect of onabotulinumtoxinA (5–7 units) in rats. The authors noted that their results provided evidence for a central mode of action for botulinum toxin-A in this pain model. They also demonstrated that intraperitoneal injection of bicuculline ($P < 0.05$) reversed the reduction of mechanical pain induced by BoNT-A. Since injection of bicuculline into cisterna magna did not reverse the effect of botulinum toxin-A, authors concluded that the effect of botulinum toxin must be at the spinal level (not supraspinal), and is partly mediated by inhibition of GABA effect centrally.

Effects of Botulinum Toxins on Opioid Channels

Opioid Receptors

Opioid receptors are present in abundance in the brain and spinal cord and play a major role in pain modulation. Endogenous opioids include dynorphins, enkephalins, endomorphins, and nociceptin. Among several described kinds of opioid receptors, μ opioid receptors are most widely distributed in the peripheral and central nervous systems (brain, brain stem, and spinal cord).

Drinovac et al. [56] studied the potential role of opioid receptors in BTX-A's antinociceptive activity in rat's formalin pain model. As described previously in this chapter, pretreatment with BoNTs-A and B in this model alleviates local pain and reduces local accumulation of glutamate. To assess the effect of the opioid system on BoNT's antinociceptive role in this model, the authors injected opioid antagonist naltrexone subcutaneously (0.02–2 mg/kg) or intrathecally (0.07 μg/10 μl–350 μg/10 μl) in some rats, while other rats received selective μ-antagonist naloxonazine intraperitoneally (5 mg/kg). The influence of naltrexone (2 mg/kg s.c.) on BoNT-A antinociceptive activity was also additionally examined in partial sciatic nerve transection induced experimental painful neuropathy. The authors found that antinociceptive effects of BoNT-A in formalin and sciatic nerve transection-induced pain were prevented by nonselective opioid antagonist naltrexone. Additionally, the pain-reducing effect of BoNT-A in this model was abolished by low dose of intrathecal naltrexone and by selective μ-antagonist naloxonazine. The decrease in dorsal horn's c-Fos expression caused by BoNT-A injection was also prevented by injection of naltrexone. Prevention of BoNT-A effects on pain and c-Fos expression by opioid antagonists suggested to the authors that the central antinociceptive action of BoNT-A might be associated with the activity of endogenous opioid system (involving μ-opioid receptor).

BoNT Effects on Nerve Regeneration and Nerve Recovery

Mice suffering from neuropathic pain and allodynia secondary to sciatic nerve ligation demonstrate quicker recovery of walking pattern after intraplantar, intrathecal, or intraperitoneal injection of 15 pg/kg of onabotulinumtoxinA [57]. In this experiment, authors used expression of S100β protein and glial fibrillary acidic protein (GFAP) by immunofluorescence to illustrate the changes in the sciatic nerve; there was evidence for structural modification such as expression of cell division cycle 2 and growth-associated protein 43 (GAP-43) regeneration-associated proteins which suggested treatment with onabotulinumtoxinA facilitates nerve recovery. Lima et al. [58] also found that when compared with controls, transected tibial nerve also recovered faster in rats injected with BoNT-A into the gastrocnemius muscle. In

another study [59], using a similar mouse model of peripheral nerve injury, authors noted that injection of BoNT-B improved pain behavior but failed to promote functional recovery. Cobianchi et al. [60] assessed the effect of low-dose (15 pg) intraplantar injection of BoNT-A in mice after inducing chronic constriction injury (CCI) of the sciatic nerve. They noted regrowing myelinated axons and increase in reinnervation of gastrocnemius and plantar muscles of the injected mouse compared to controls. Franz et al. [61] tested the effects of BoNT-A in mouse model of tibial nerve injury and human stem cells. Injection of BoNT into triceps surae of the mouse, 1 week before afflicting injury to the animal, resulted in significantly enhanced outgrowth of murine motor axons as well as the human motor neuron neurites tested in vitro (upon exposure to BoNT).

In a recent publication, Vacca et al. [62] reported on the effect of spinal injection of BoNT-A (between L4-L5 vertebrae) on the motor function of mice after induced traumatic spinal cord injury at T10–T11 level. BoNT-A was injected 1 h after induced injury. The dose of injected BoNT-A was 15 pg/5 μL corresponding to 7.5 μ/kg of Botox (onabotulinumtoxinA). The results from toxin-injected mice were compared with a group of mice injected with saline at the same level. Motor recovery was assessed by the Bosco Mouse Scale (BMS) and spinal reflex by tail-flick test.

All animals demonstrated absence of hind limb movements at day one after cord injury. On day four, gradual return of function was noted only in the BoNT-treated mice. At day 30 post injury, all subjects in the BoNT-injected group demonstrated complete recovery from paralysis, whereas all mice in the saline-injected group remained still paralyzed ($P < 0.000$). Mice injected with BoNT-A regained thermal sensitivity at day 20 post injection, but the saline-injected mice totally lost thermal sensitivity in the hind limb. The mechanical threshold for neuropathic pain was reduced in mice after injury and remained reduced only in the saline group ($P = 0.007$). Examination of the tissue showed less scar formation and considerably less spinal cord atrophy in the toxin-injected group ($P < 0001$). In the toxin-injected group, 30 days after injury, motor neurons were preserved in the spinal cord below the level of injury and survived, whereas they did not in the saline-injected group ($P = 0.0036$). Vesicular transporter of glutamate 1, a marker of neural excitability, was found significantly decreased in the toxin-injected group ($P = 0.0013$). The authors suggested that retrograde transfer of the toxin from the site of injection to the site of injury accounted to the BoNT-A's protective and regenerative action. In the authors' words, "their study demonstrated an extraordinary ability for BoNT-A for neuroprotection and CNS regeneration." The experiment also showed the BoNT-A's potential for reducing neuropathic pain after spinal cord injury. The figure from their article demonstrates the site of injection and the cascade of events that followed at the cellular level following BoNT-A injection leading to the toxin's effect (Fig. 3.4). Luvisetto [63] has recently reviewed the emerging literature on the role of BoNT's injection on enhancing the regeneration and recovery of injured nerves and emphasized the potential of BoNTs in treatment of pain caused by central or peripheral trauma.

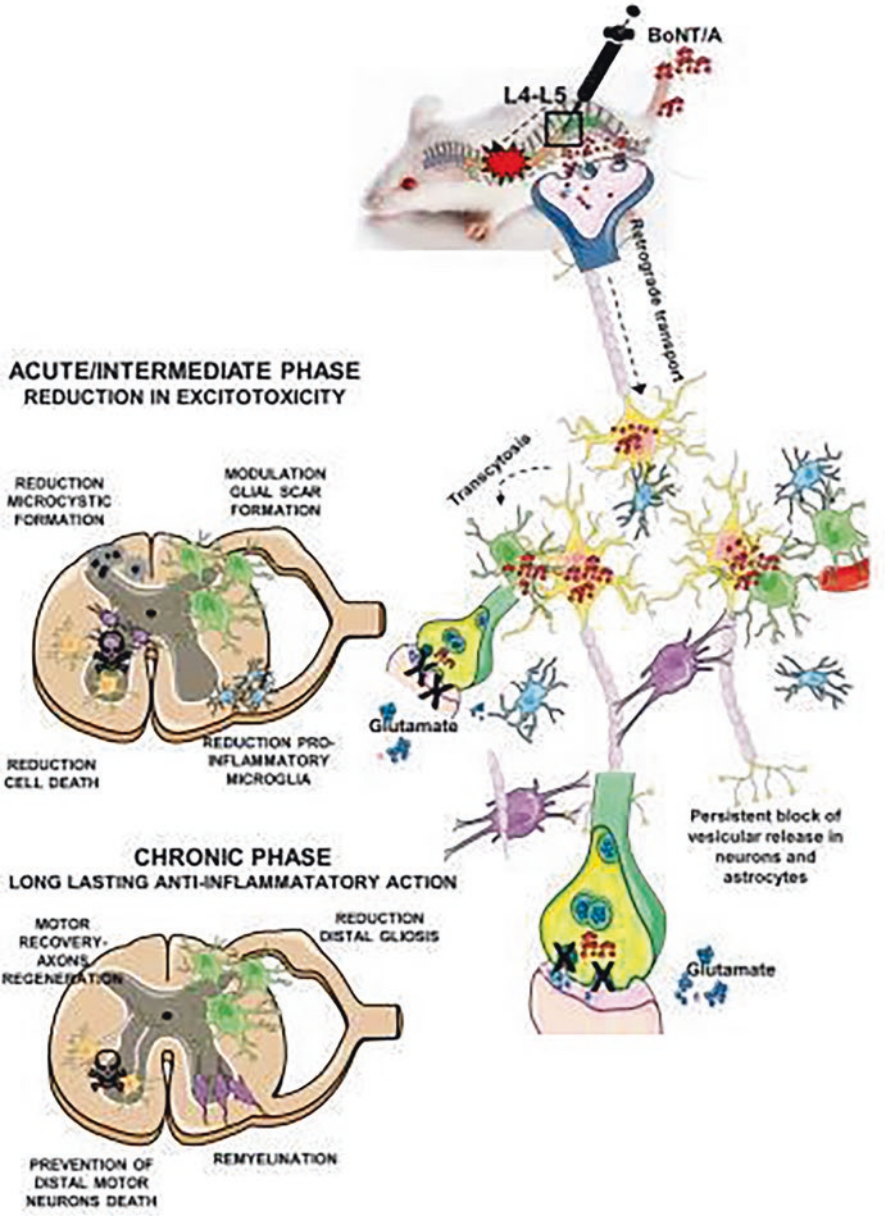

Fig. 3.4 Acute and chronic phase of nerve injury from Vacca et al. [62]. Published in Toxins. Reproduced with permission from Publisher PMC

Evidence for Central Analgesic Effect of Botulinum Neurotoxins

Emerging data from in vitro and in vivo studies suggest that analgesic effect of BoNTs is, at least partly, related to their role on central nociceptive pathways [64–66]. This information comes mainly from two lines of evidence:

1. Data suggesting that the active moiety of peripherally injected BoNT travels along the peripheral nerve to the central nervous system.

This process has been demonstrated convincingly for motor neurons by Caleo and his colleagues in a recent experiment [67]. They have shown that catalytically active BoNT-A was transported to the facial nucleus (FN) in the pons after injection into the nasolabial musculature of rats and mice. BoNT-A-mediated cleavage of SNAP-25 in the FN was prevented by intraventricular delivery of antitoxin antibodies, indicating that BoNT-A physically left the motor neurons to enter second-order neurons. Analysis of nerve terminals within the FN showed that BoNT-A was transcytosed preferentially into cholinergic synapses.

In the sensory system, Matak et al. [68] have found cleaved SNAP-25 in spinal trigeminal nucleus caudalis and oralis after injecting BoNT-A into the rats' whisker pad. In the optic system, after injection of BoNT-A into the rat's eye, catalytically active, cleaved SNAP 25 appears in abundance in the superior colliculus (upper brain stem) and is transcytosed into the tectal synapses [69]. This transfer of toxin, after peripheral injection into the central nervous system, appears to be an active and energy-dependent process [64–69]. Indirect evidence for central effect of BoNT has been provided by the studies that have shown enhanced expression of c-fos and production of pain transmitters such as substance P and CGRP following peripheral injection of BoNT-B into spinal sensory neurons [11].

2. Data from animal and human (asymptomatic volunteers) studies demonstrating improvement of bilateral limb pain after unilateral injection of BoNT.

Much of the data have been provided by the investigators of the Department of Pharmacology in the University of Zagreb in Croatia. Development of bilateral pain (mirror pain), after development of unilateral pain caused by exposure to noxious agents, is a curious phenomenon which has been shown to develop after unilateral injection/exposure of a nociceptive agent such as acidic saline [70]. Back-Rojecky and Lackovic [71] have shown that in the acid saline model of bilateral pain, unilateral injection of 5 units of BoNT-A into the sciatic nerve on the side of saline injection improved pain bilaterally. This effect was blocked by injection of colchicine which prevents axonal transport. In another study, the same group of investigators [72] showed that unilateral injection of BoNT-A can reduce pain behavior bilaterally in rats with bilateral painful diabetic neuropathy. Similar bilateral effect after unilateral injection was also induced by abobotulinumtoxinA (Dysport) injection in the case of bilateral carrageenan-induced peripheral neuropathy [73, 74]. The

above-mentioned data in mirror pain support the notion that the analgesic effects of BoNTs are partly conducted through a central effect.

Additional Mechanisms Potentially Promoting the Analgesic Effects of BoNTs in Pain

Fillipi et al. [75] have shown that injection of BoNT-A into jaw muscles of the rat substantially reduces the discharge of muscle spindles. Since muscle spindles provide a major sensory input into the spinal cord, and inhibiting this input can reduce the central sensitization caused by chronic pain. Local injection of BoNTs also impairs sympathetic transmission which is believed to contribute to pain chronicity and maintenance (sympathetically maintained pain) [76].

Conclusion

Botulinum neurotoxins exert an analgesic effect through a myriad of different mechanisms**.** These include inhibitory actions upon pain receptors and pain transmitters as well interference with inflammatory cascades that are at work in several pain states. In addition to their well-known peripheral analgesic effect, the emerging data have shown that after peripheral injection, the active moiety of the botulinum toxin is transported to the central nervous system suggesting an additional central analgesic effect. The animal data demonstrating the role of BoNT injection in neural regeneration and protection after spinal cord injury have major implications in human subjects both for recovery after injury and reduction of posttraumatic pain.

References

1. Tam MF, Loh YC, Tan CS, Khadijah Adam S, Abdul Manan N, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018;19(8):2164. https://doi.org/10.3390/ijms19082164. PMID: 30042373; PMCID: PMC6121522
2. Priestley JV, Michael GJ, Averill S, Liu M, Willmott N. Regulation of nociceptive neurons by nerve growth factor and glial cell line derived neurotrophic factor. Can J Physiol Pharmacol. 2002;80(5):495–505. https://doi.org/10.1139/y02-034. PMID: 12056559
3. Neumann S, Doubell TP, Leslie T, Woolf CJ. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature. 1996;384(6607):360–4. https://doi.org/10.1038/384360a0. PMID: 8934522
4. Bourne S, Machado AG, Nagel SJ. Basic anatomy and physiology of pain pathways. Neurosurg Clin N Am. 2014;25(4):629–38. https://doi.org/10.1016/j.nec.2014.06.001. Epub 2014 Aug 3. PMID: 25240653

5. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971–9. https://doi.org/10.1126/science.150.3699.971. PMID: 5320816
6. Anderson WS, O'Hara S, Lawson HC, Treede RD, Lenz FA. Plasticity of pain-related neuronal activity in the human thalamus. Prog Brain Res. 2006;157:353–64. https://doi.org/10.1016/S0079-6123(06)57021-9. PMID: 17046675
7. Lenz FA, Weiss N, Ohara S, Lawson C, Greenspan JD. The role of the thalamus in pain. Suppl Clin Neurophysiol. 2004;57:50–61. https://doi.org/10.1016/s1567-424x(09)70342-3. PMID: 16106605
8. Rosenow JM, Henderson JM. Anatomy and physiology of chronic pain. Neurosurg Clin N Am. 2003;14(3):445–62, vii. https://doi.org/10.1016/s1042-3680(03)00009-3. PMID: 14567145
9. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107:125–33.
10. Wheeler-Aceto H, Porreca F, Cowan A. The rat paw formalin test: comparison of noxious agents. Pain. 1990;40:229–38.
11. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155:674–84.
12. Welch MJ, Purkis JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. Toxicon. 2000;38:245–58.
13. Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int. 2008;101:366–70.
14. Meng J, Wang J, Lawrence G, Dolly JO. Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. J Cell Sci. 2007;120:2864–74.
15. Meng J, Ovsepian SV, Wang J, Pickering M, Sasse A, Aoki KR, Lawrence GW, Dolly JO. Activation of TRPV1 mediates calcitonin gene-related peptide release, which excites trigeminal sensory neurons and is attenuated by a retargeted botulinum toxin with anti-nociceptive potential. J Neurosci. 2009;29:4981–92.
16. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the anti-nociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;358:137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 Jul 1. PMID: 28673722
17. Tang M, Meng J, Wang J. New engineered-botulinum toxins inhibit the release of pain-related mediators. Int J Mol Sci. 2019;21(1):262. https://doi.org/10.3390/ijms21010262. PMID: 31906003; PMCID: PMC6981458
18. Joussain C, Le Coz O, Pichugin A, Marconi P, Lim F, Sicurella M, Salonia A, Montorsi F, Wandosell F, Foster K, Giuliano F, Epstein AL, Aranda MA. Botulinum neurotoxin light chains expressed by defective herpes simplex virus type-1 vectors cleave SNARE proteins and inhibit CGRP release in rat sensory neurons. Toxins (Basel). 2019;11(2):123. https://doi.org/10.3390/toxins11020123. PMID: 30791373; PMCID: PMC6409900
19. Fischer TZ, Waxman SG. Familial pain syndromes from mutations of the NaV1.7 sodium channel. Ann N Y Acad Sci. 2010;1184:196–207.
20. Shin MC, Wakita M, Xie DJ, Yamaga T, Iwata S, Torii Y, Harakawa T, Ginnaga A, Kozaki S, Akaike N. Inhibition of membrane Na+ channels by A type botulinum toxin at femtomolar concentrations in central and peripheral neurons. J Pharmacol Sci. 2012;118(1):33–42. https://doi.org/10.1254/jphs.11060fp. Epub 2011 Dec 10. PMID: 22156364
21. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D (October 1997). "The capsaicin receptor: a heat-activated ion channel in the pain pathway". Nature 389: 816–824.
22. Schaible HG. Peripheral and central mechanisms of pain generation. Handb Exp Pharmacol. 2007;177:3–28.

23. Kumamoto E, Fujita T, Jiang CY. TRP channels involved in spontaneous L-glutamate release enhancement in the adult rat spinal substantia gelatinosa. Cell. 2014;3:331–62.
24. Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P, Harries MH, Latcham J, Clapham C, Atkinson K, et al. Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. Nature. 2000;405:183–7.
25. Watabiki T, Kiso T, Tsukamoto M, Aoki T, Matsuoka N. Intrathecal administration of AS1928370, a transient receptor potential vanilloid 1 antagonist, attenuates mechanical allodynia in a mouse model of neuropathic pain. Biol Pharm Bull. 2011;34:1105–8.
26. Obata K, Katsura H, Mizushima T, Yamanaka H, Kobayashi K, Dai Y, Fukuoka T, Tokunaga A, Tominaga M, Noguchi K. TRPA1 induced in sensory neurons contributes to cold hyperalgesia after inflammation and nerve injury. J Clin Invest. 2005;115:2393–401.
27. Xiao L, Cheng J, Zhuang Y, Qu W, Muir J, Liang H, Zhang D. Botulinum toxin type A reduces hyperalgesia and TRPV1 expression in rats with neuropathic pain. Pain Med. 2013;14(2):276–86. https://doi.org/10.1111/pme.12017. Epub 2013 Jan 10. PMID: 23301515
28. Shimizu T, Shibata M, Toriumi H, Iwashita T, Funakubo M, Sato H, Kuroi T, Ebine T, Koizumi K, Suzuki N. Reduction of TRPV1 expression in the trigeminal system by botulinum neurotoxin type-A. Neurobiol Dis. 2012;48(3):367–78. https://doi.org/10.1016/j.nbd.2012.07.010. Epub 2012 Jul 20. PMID: 22820141
29. Zhang Y, Su Q, Lian Y, Chen Y. Botulinum toxin type A reduces the expression of transient receptor potential melastatin 3 and transient receptor potential vanilloid type 4 in the trigeminal subnucleus caudalis of a rat model of trigeminal neuralgia. Neuroreport. 2019;30(10):735–40. https://doi.org/10.1097/WNR.0000000000001268. PMID: 31116130
30. Nugent M, Yusef YR, Meng J, Wang J, Dolly JO. A SNAP-25 cleaving chimera of botulinum neurotoxin /A and /E prevents TNFα-induced elevation of the activities of native TRP channels on early postnatal rat dorsal root ganglion neurons. Neuropharmacology. 2018;138:257–66. https://doi.org/10.1016/j.neuropharm.2018.06.016. Epub 2018 Jun 12. PMID: 29906413
31. Snider WD, McMahon SB. Tackling pain at the source: new ideas about nociceptors. Neuron. 1998;20:629–32.
32. Apostolidis A, Popat R, Yiangou Y, Cockayne D, Ford AP, Davis JB, Dasgupta P, Fowler CJ, Anand P. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol 2005;174(3):977–982; discussion 982-3. https://doi.org/10.1097/01.ju.0000169481.42259.54. PMID: 16094018.
33. Xiao L, Cheng J, Dai J, Zhang D. Botulinum toxin decreases hyperalgesia and inhibits P2X3 receptor over-expression in sensory neurons induced by ventral root transection in rats. Pain Med. 2011;12(9):1385–94. https://doi.org/10.1111/j.1526-4637.2011.01182.x. Epub 2011 Aug 2. PMID: 21810163
34. Liu HT, Chen SH, Chancellor MB, Kuo HC. Presence of cleaved synaptosomal-associated protein-25 and decrease of purinergic receptors P2X3 in the bladder urothelium influence efficacy of botulinum toxin treatment for overactive bladder syndrome. PLoS One. 2015;10(8):e0134803. https://doi.org/10.1371/journal.pone.0134803. PMID: 26241848; PMCID: PMC4524624
35. Donnerer J, Schuligoi R, Stein C, Amann R. Upregulation, release and axonal transport of substance P and calcitonin gene-related peptide in adjuvant inflammation and regulatory function of nerve growth factor. Regul Pept. 1993;46(1–2):150–4. PMID: 7692483
36. Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD, Brown MT. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med. 2010;363:1521–31.
37. McMahon SB, Bennet DLH, Bevan S. Inflammatory mediators and modulators. In: McMahon SB, Koltzenburg M, editors. Wall and Melzack's textbook of pain. Edinburgh: Elsevier Churchill Livingstone; 2006. p. 49–72.
38. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology. 2005;26:785–93.

39. Attal N, de Andrade DC, Adam F, Ranoux D, Teixeira MJ, Galhardoni R, Raicher I, Üçeyler N, Sommer C, Bouhassira D. Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2016;15(6):555–65. https://doi.org/10.1016/S1474-4422(16)00017-X. Epub 2016 Mar 2. PMID: 26947719
40. Bach-Rojecky L, Dominis M, Lacković Z. Lack of anti-inflammatory effect of botulinum toxin type A in experimental models of inflammation. Fundam Clin Pharmacol. 2008;22(5):503–9. https://doi.org/10.1111/j.1472-8206.2008.00615.x. Epub 2008 Aug 20. PMID: 18717739
41. Bittencourt da Silva L, Karshenas A, Bach FW, Rasmussen S, Arendt-Nielsen L, Gazerani P. Blockade of glutamate release by botulinum neurotoxin type A in humans: a dermal microdialysis study. Pain Res Manag. 2014;19(3):126–32. https://doi.org/10.1155/2014/410415. PMID: 24851237; PMCID: PMC4158957
42. Wang L, Wang K, Chu X, Li T, Shen N, Fan C, Niu Z, Zhang X, Hu L. Intra-articular injection of Botulinum toxin A reduces neurogenic inflammation in CFA-induced arthritic rat model. Toxicon. 2017;126:70–8. https://doi.org/10.1016/j.toxicon.2016.11.009. Epub 2016 Nov 9. PMID: 27838288
43. Yoo KY, Lee HS, Cho YK, Lim YS, Kim YS, Koo JH, Yoon SJ, Lee JH, Jang KH, Song SH. Anti-inflammatory effects of botulinum toxin type A in a complete Freund's adjuvant-induced arthritic knee joint of hind leg on rat model. Neurotox Res. 2014;26:32–9.
44. Chuang YC, Yoshimura N, Huang CC, Wu M, Chiang PH, Chancellor MB. Intravesical botulinum toxin A administration inhibits COX-2 and EP4 expression and suppresses bladder hyperactivity in cyclophosphamide-induced cystitis in rats. Eur Urol. 2009;56(1):159–66. https://doi.org/10.1016/j.eururo.2008.05.007. Epub 2008 May 20. PMID: 18514386
45. Chuang Y-C, Yoshimura N, Huang C-C, Wu M, Chiang P-H, Chancellor MB. Intraprostatic botulinum toxin a injection inhibits cyclooxygenase-2 expression and suppresses prostatic pain on capsaicin induced prostatitis model in rat. J Urol. 2008;180:742–8.
46. Namazi H. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis: a molecular mechanism. Urology. 2008;72:463–4.
47. Chuang YC, Yoshimura N, Huang CC, et al. Intraprostatic botulinum toxin a injection inhibits cyclooxygenase-2 expression and suppresses prostatic pain on capsaicin induced prostatitis model in rat. J Urol. 2008;180:742–8.
48. Wang X, Tian S, Wang H, Liu P, Zheng H, Wu L, Liu Q, Wu W. Botulinum toxin type A alleviates neuropathic pain and suppresses inflammatory cytokines release from microglia by targeting TLR2/MyD88 and SNAP23. Cell Biosci. 2020;10(1):141. https://doi.org/10.1186/s13578-020-00501-4. PMID: 33298171; PMCID: PMC7724852
49. Shi X, Gao C, Wang L, Chu X, Shi Q, Yang H, Li T. Botulinum toxin type A ameliorates adjuvant-arthritis pain by inhibiting microglial activation-mediated neuroinflammation and intracellular molecular signaling. Toxicon. 2020;178:33–40. https://doi.org/10.1016/j.toxicon.2019.12.153. Epub 2019 Dec 23. PMID: 32250746
50. Manuel Muñoz-Lora VR, Abdalla HB, Del Bel Cury AA, Clemente-Napimoga JT. Modulatory effect of botulinum toxin type A on the microglial P2X7/CatS/FKN activated-pathway in antigen-induced arthritis of the temporomandibular joint of rats. Toxicon. 2020;187:116–21. https://doi.org/10.1016/j.toxicon.2020.08.027. Epub 2020 Sep 1. PMID: 32882256
51. Mika J, Rojewska E, Makuch W, Korostynski M, Luvisetto S, Marinelli S, Pavone F, Przewlocka B. The effect of botulinum neurotoxin A on sciatic nerve injury-induced neuroimmunological changes in rat dorsal root ganglia and spinal cord. Neuroscience. 2011;175:358–66. https://doi.org/10.1016/j.neuroscience.2010.11.040. Epub 2010 Nov 25. PMID: 21111791
52. Vacca V, Marinelli S, Luvisetto S, Pavone F. Botulinum toxin A increases analgesic effects of morphine, counters development of morphine tolerance and modulates glia activation and μ opioid receptor expression in neuropathic mice. Brain Behav Immun. 2013;32:40–50.
53. Zychowska M, Rojewska E, Makuch W, Luvisetto S, Pavone F, Marinelli S, Przewlocka B, Mika J. Participation of pro- and anti-nociceptive interleukins in botulinum toxin A-induced

analgesia in a rat model of neuropathic pain. Eur J Pharmacol. 2016;791:377–88. https://doi.org/10.1016/j.ejphar.2016.09.019. Epub 2016 Sep 9. PMID: 27619001
54. Bardoni R, Takatawa T, Tong CK, Choudhury P, Scherre G, MacDermott AB. Pre- and postsynaptic inhibitory control in the spinal cord dorsal horn. Ann N Y Acad Sci. 2013;1279:90–6.
55. Drinovac V, Bach-Rojecky L, Lacković Z. Association of antinociceptive action of botulinum toxin type A with GABA-A receptor. J Neural Transm (Vienna). 2014;121(6):665–9. https://doi.org/10.1007/s00702-013-1150-6. Epub 2014 Jan 14. PMID: 24420081
56. Drinovac V, Bach-Rojecky L, Matak I, Lacković Z. Involvement of μ-opioid receptors in antinociceptive action of botulinum toxin type A. Neuropharmacology. 2013;70:331–7. https://doi.org/10.1016/j.neuropharm.2013.02.011. Epub 2013 Mar 13. PMID: 23499661
57. Marinelli S, Luvisetto S, Cobianchi S, Makuch W, Obara I, Mezzaroma E, Caruso M, Straface E, Przewlocka B, Pavone F. Botulinum neurotoxin type A counteracts neuropathic pain and facilitates functional recovery after peripheral nerve injury in animal models. Neuroscience. 2010;171(1):316–28. https://doi.org/10.1016/j.neuroscience.2010.08.067. Epub 2010 Sep 6. PMID: 20826198
58. Lima W, Salles AG, Faria JCM, Nepomuceno AC, Salomone R, Krunn P, Gemperli R. Contralateral botulinum toxin improved functional recovery after tibial nerve repair in rats. Plast Reconstr Surg. 2018;142(6):1511–9. https://doi.org/10.1097/PRS.0000000000004981. PMID: 30188467
59. Finocchiaro A, Marinelli S, De Angelis F, Vacca V, Luvisetto S, Pavone F. Botulinum toxin B affects neuropathic pain but not functional recovery after peripheral nerve injury in a mouse model. Toxins (Basel). 2018;10(3):128. https://doi.org/10.3390/toxins10030128. PMID: 29562640; PMCID: PMC5869416
60. Cobianchi S, Jaramillo J, Luvisetto S, Pavone F, Navarro X. Botulinum neurotoxin A promotes functional recovery after peripheral nerve injury by increasing regeneration of myelinated fibers. Neuroscience. 2017;359:82–91. https://doi.org/10.1016/j.neuroscience.2017.07.011. Epub 2017 Jul 14. PMID: 28716587
61. Franz CK, Puritz A, Jordan LA, Chow J, Ortega JA, Kiskinis E, Heckman CJ. Botulinum toxin conditioning enhances motor axon regeneration in mouse and human preclinical models. Neurorehabil Neural Repair. 2018;32(8):735–45. https://doi.org/10.1177/1545968318790020. Epub 2018 Jul 25. PMID: 30043670; PMCID: PMC7359633
62. Vacca V, Madaro L, De Angelis F, Proietti D, Cobianchi S, Orsini T, Puri PL, Luvisetto S, Pavone F, Marinelli S. Revealing the therapeutic potential of botulinum neurotoxin type A in counteracting paralysis and neuropathic pain in spinally injured mice. Toxins (Basel). 2020;12(8):491. https://doi.org/10.3390/toxins12080491. PMID: 32751937; PMCID: PMC7472120
63. Luvisetto S. Botulinum toxin and neuronal regeneration after traumatic injury of central and peripheral nervous system. Toxins (Basel). 2020;12(7):434. https://doi.org/10.3390/toxins12070434. PMID: 32630737; PMCID: PMC7404966
64. Rossetto O, Pirazzini M, Fabris F, Montecucco C. Botulinum neurotoxins: mechanism of action. Handb Exp Pharmacol. 2021;263:35–47. https://doi.org/10.1007/164_2020_355. PMID: 32277300
65. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: biology, pharmacology, and toxicology. Pharmacol Rev. 2017;69(2):200–35. https://doi.org/10.1124/pr.116.012658. PMID: 28356439; PMCID: PMC5394922
66. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459. PMID: 31387301; PMCID: PMC6723487
67. Caleo M, Spinelli M, Colosimo F, Matak I, Rossetto O, Lackovic Z, Restani L. Transynaptic action of botulinum neurotoxin type A at central cholinergic boutons. J Neurosci. 2018;38(48):10329–37. https://doi.org/10.1523/JNEUROSCI.0294-18.2018. Epub 2018 Oct 12. PMID: 30315128; PMCID: PMC6596210

68. Matak I, Rossetto O, Lacković Z. Botulinum toxin type A selectivity for certain types of pain is associated with capsaicin-sensitive neurons. Pain. 2014;155(8):1516–26. https://doi.org/10.1016/j.pain.2014.04.027. Epub 2014 May 2. PMID: 24793910
69. Restani L, Antonucci F, Gianfranceschi L, Rossi C, Rossetto O, Caleo M. Evidence for anterograde transport and transcytosis of botulinum neurotoxin A (BoNT/A). J Neurosci. 2011;31(44):15650–9. https://doi.org/10.1523/JNEUROSCI.2618-11.2011. PMID: 22049408; PMCID: PMC6623022
70. Sluka KA, Kalra A, Moore SA. Unilateral intramuscular injections of acidic saline produce a bilateral, long-lasting hyperalgesia. Muscle Nerve. 2001;24(1):37–46. https://doi.org/10.1002/1097-4598(200101)24:1<37::aid-mus4>3.0.co;2-8. PMID: 11150964
71. Bach-Rojecky L, Lacković Z. Central origin of the antinociceptive action of botulinum toxin type A. Pharmacol Biochem Behav. 2009;94(2):234–8. https://doi.org/10.1016/j.pbb.2009.08.012. Epub 2009 Sep 2. PMID: 19732788
72. 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(1–3):10–4. https://doi.org/10.1016/j.ejphar.2010.01.020. Epub 2010 Feb 1. PMID: 20123097
73. Favre-Guilmard C, Chabrier PE, Kalinichev M. Bilateral analgesic effects of abobotulinumtoxinA (Dysport®) following unilateral administration in the rat. Eur J Pain. 2017;21(5):927–37. https://doi.org/10.1002/ejp.995. Epub 2017 Mar 6. PMID: 28263010
74. Lackovic Z. Botulinum toxin and pain. In: Hallet, Whitcomb, editors. Botulinum toxin. Springer; 2020. p. 256–7.
75. 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. https://doi.org/10.3109/00016489309135834. PMID: 8390772
76. Rand MJ, Whaler BC. Impairment of sympathetic transmission by botulinum toxin. Nature. 1965;206(984):588–91. https://doi.org/10.1038/206588a0. PMID: 5319286

Chapter 4
Botulinum Toxin Therapy for Neuropathic Pain (NP)

Neuropathic Pain: Definition and Pathophysiology

Neuropathic pain (NP) is defined as a pain caused by a lesion or disease of the somatosensory system [1]. The site of disturbance or damage can be peripheral (peripheral nerve, plexus, or root) or central (spinal cord, brain stem, or thalamus). Typically, the pain has a burning, jabbing, and searing quality. Skin areas of allodynia (touch perceived as pain), hyperalgesia (enhanced pain after exposure to painful stimuli), and hyperesthesia or dysesthesia (enhanced or altered sensations to touch) are common in neuropathic pain.

The exact pathophysiology of neuropathic pain is yet to be fully elucidated; peripheral neuropathic pain (PNP) is currently believed to result from damage to peripheral nervous system with irritation of nerve endings leading to accumulation of nociceptive transmitters and modulators (substance P, glutamate, bradykinin, calcitonin gene-related peptide, and others) at nerve endings and dorsal root ganglia. Accumulation of these agents produces local inflammation. Together, these two phenomena lower the sensory threshold of peripheral nerve endings to nociceptive stimuli (peripheral sensitization). Peripheral sensitization increases the number of nociceptive volleys into the spinal cord and leads to sensitization of sensory spinal cord neurons (central sensitization). The interplay between peripheral and central sensitization contributes to pain chronicity [2].

A number of mechanisms are now considered as contributors to neuropathic pain (Table 4.1) [3]. Modifying these mechanisms is the basis of strategies for NP therapy. OnabotulinumtoxinA and B have shown the potential to alleviate pain in animals through a number of mechanisms. These mechanisms which are both peripheral and central were discussed in detail in Chap. 2 of this book.

This chapter discusses the current treatment of three common categories of neuropathic pain and reviews the literature on the efficacy of botulinum neurotoxin (BoNT) therapy in three pain disorders. These pain disorders include postherpetic

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_4

neuralgia, posttraumatic neuralgia, and painful diabetic neuropathy. Trigeminal neuralgia, another form of neuropathic pain, is discussed in the chapter on facial pain disorders (Chap. 10); other forms of neuropathic pains are discussed as individual chapters in this book. Observations on complex regional pain syndrome, chemotherapy-induced pain, and residual pain after amputation are also briefly discussed at the end of this chapter.

In this chapter and throughout this book, the level of efficacy for BoNTs is defined according to the guidelines of the Therapeutics and Assessment Subcommittee of the American Academy of Neurology (AAN). These guidelines require two class I studies for level A evidence (effective or not effective). For level B evidence (probably effective/ineffective), one class I or two class II studies are required. Presence of only one class II study denotes a level C (possibly effective/ineffective) evidence. Level U means efficacy is undetermined [4, 5].

Currently, out of 7 well-defined serological types of botulinum neurotoxins (A to G), only types A and B are approved by the FDA for clinical practice. Among type A toxins, onabotulinumtoxinA (Botox), incobotulinumtoxinA (Xeomin), and abobotulinumtoxinA (Dysport) are widely used in the United States for different clinical conditions. The composition and serological characteristics of these toxins, as well as a their preparation for use, were discussed in Chap. 2.

Postherpetic Neuralgia (PHN)

Herpes zoster (zoster in Greek meaning belt) results from reactivation of varicela-zoster (VZ) virus usually in individuals who previously have had chicken pox and developed cell-mediated immunity after the infection. The reactivation takes place in cranial nerves or dorsal root ganglia with the spread of the virus to sensory nerves and corresponding dermatome. Diabetic and immunocompromised patients are more prone to zoster infection.

The extent of pathology varies widely from patient to patient. There is often substantial reduction of epidermal nerve fibers (small unmyelinated fibers) and loss of subepidermal plexus. Reinnervation is slow, and skin biopsy, even 10 years after the infection, shows incomplete innervation [6]. In one study, magnetic resonance imaging showed signal changes in the spinal cord and brain stem (56%) and cerebrospinal fluid demonstrated inflammatory cells in 61% of the patients affected by acute zoster infection [6]. Varicella-zoster vaccination with older vaccine (Zostavax) reduces development of PHN by 66.5% between ages 60 and 80 years [7]. According to Center of Disease Control (CDC), the newer zoster vaccine (Shingrix) that requires two injections, few months apart, is more than 90% effective to prevent shingles and postherpetic neuralgia. Antiviral therapy reduces the risk of developing PHN [8]. The concurrent steroid therapy does not reduce the risk of PHN but alleviates the initial acute pain [9].

The rash of herpes zoster is typically in the distribution of peripheral nerves (Fig. 4.1). Pain associated with zoster infection may manifest before the rash

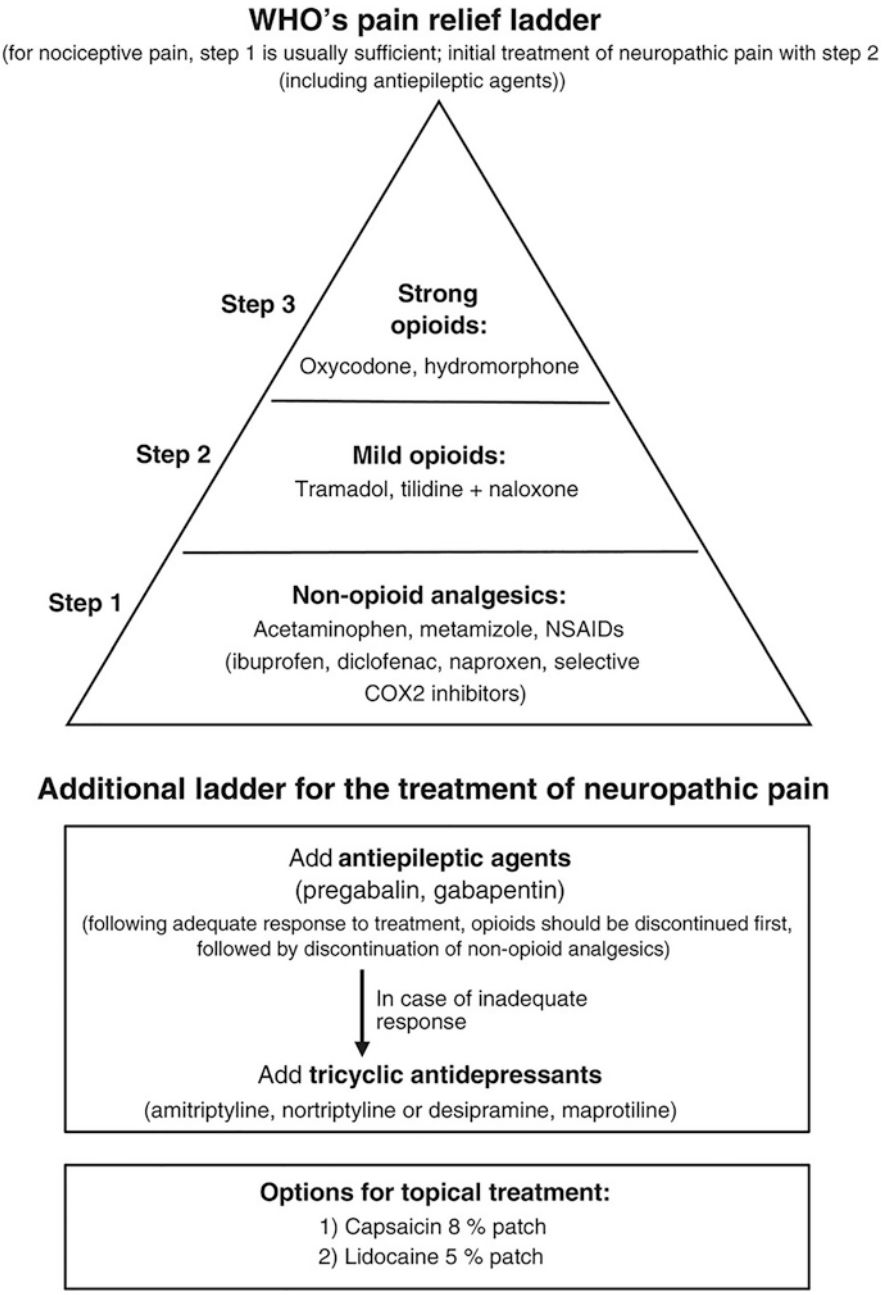

Fig. 4.1 WHO pain ladder for treatment of postherpetic neuralgia

(presymptomatic neuralgia), during the rash, or even later after the rash has cleared up. The typical PHN usually persists beyond 3 months after the zoster infection. The incidence of postherpetic neuralgia increases with age: 5% for individuals younger than 60 years of age, 10% for those between 60 and 69, and 20% for those 80 years of age or older [10]. Older age, severity of the initial acute pain [11], presence of larger fiber neuropathy (A-beta fibers with loss of vibration) [12], and slow clearance of the virus from saliva [13]) increase the risk of PHN. A recent meta-analysis of published literature has shown that presence of extensive skin rashes and ophthalmic herpes also correlates with higher incidence of postherpetic neuralgia [14].

Treatment

PHN is one of the most severe forms of human pain. Affected individuals cope with poor quality of life and are often disabled by severe bouts of pain [15]. Approximately, 40% of the patients with PTN consider their pain as severe [16]. A variety of oral and topical medications are currently in use for treatment of PHN [17]. Medical treatment includes the use of topical anesthetics, tricyclic antidepressants, gabaergic medications, steroids, and opioid analgesics. Among topical analgesics, lidocaine patch 0.5% (every 12 or 24 h) is commonly used. It should be applied only to intact skin. Nortriptyline can be started at a daily dose of 25 mg and increased by 25 mg daily (up to 150 mg, if tolerated). Gabapentin and pregabalin, due to their safer side effect profiles, are often used as first-line drugs sometimes in combination with tricyclic agents. The starting dose is 300 mg and 75 mg at bedtime for these two drugs, respectively. The dose can be escalated gradually to a maximum of 3600 for gabapentin and a maximum of 600 for pregabalin in patients suffering from severe pain. In a recent study published from Mayo clinic, authors have shown that the incidence of postherpetic neuralgia was significantly lower in patients with diabetic and non-diabetic painful neuropathies who had been treated with gabapentin prior to development of herpes zoster [18]. The use of steroids is controversial due to poor tolerance by elderly. If used, the recommended regimen for prednisone is a starting dose of 60 mg for 7 days and then decreasing the dose by 15 mg every 7 days until stopping treatment. In more severe cases, postherpetic neuralgia can be treated with opioid analgesics. The starting dose of tramadol is 50 mg daily to be increased by 50 or 100 mg every 2 days to a maximum of 400 mg (300 for individuals older than 75 years). The recommended starting dose of oxycodone is 5 mg every 4 h as needed to be increased by 5 mg four times daily every 2 to 4 days. The maximum dose is not specified, but should not exceed 120 mg daily [17].

During the acute phase of pain, to prevent patients' suffering, the European and German guidelines advocate using analgesic medications for treatment of PHN according to the WHO pain relief ladder [19, 20] (Fig. 4.1). Unfortunately, a sizeable number of patients with PHN fail to respond to currently available medications. Recent reports on a limited number of patients with severe postherpetic neuralgia noted pain and itch relief after extracorporeal shock wave therapy (ECSW) [21] and

autologous fat grafting [22]. In recalcitrant cases with intractable pain, a variety of neurosurgical procedures have been tried with some degrees of success; these procedures included spinal cord stimulation (SCS), dorsal root entry zone (DREZ) lesioning, intrathecal drug delivery, dorsal root ganglion (DRG) radiofrequency lesioning, peripheral nerve stimulation, gamma knife surgery, deep brain stimulation, cordotomy, percutaneous radiofrequency rhizotomy, and Gasserian ganglion stimulation [23].

BoNT Studies in Postherpetic Neuralgia (PHN)

Two double-blind studies have investigated the efficacy of botulinum toxin-A in postherpetic neuralgia.

The first study by Xiao et al. [24] assessed pain relief by visual analog scale (VAS) at 1, 7, and 90 days after subcutaneous injection of BoNT-A in 60 patients with PHN. Quality of life was measured by improvement in sleep hours. Patients were randomized and assigned blindly into three groups: BoNT-A, lidocaine, and placebo (20 in each group). The baseline level of pain and sleep disturbance was comparable between the three groups. The location of herpetic skin lesions was orofacial ($n = 11$), cervical and upper extremity ($n = 14$), thoracic ($n = 18$) as well as lumbar and lower limbs ($n = 17$). A Chinese botulinum toxin-A prepared by Lanzhou Institute was used for this study. The injecting solution was prepared by mixing 100 units of this toxin with 2 cc of preservative-free saline (5 units/cc). Injections were subcutaneous, grid-like, 1 cm apart, and into the region of tactile allodynia. Patients in the BoNT group had significantly better pain relief compared to the two groups on lidocaine or saline ($P < 0.01$). BoNT analgesic response began at days 3 to 5, peaked at 1 week, and continued for 3 months. The improvement of sleep from BoNT was also superior compared to the lidocaine and placebo groups ($P < 0.05$). Patients in the BoNT group also used significantly less opioids (22% vs. 52% and 66% in the BoNT, lidocaine, and placebo groups, respectively). Side effects consisted only of pain at the time of injection.

Three years later, Appala et al. [25] published the results of a prospective, double-blind, parallel study comparing the effect of BoNT-A (onaA) with placebo in 30 adult subjects with PHN. In the BoNT-A group, the toxin was diluted with 4 cc of normal saline and injected subcutaneously via a 30-guage needle in a "chessboard manner." The dose per injection site was 5 units. A total of 100 units were used. The severity of pain was assessed by VAS (0–10) at baseline, and then daily for the first 2 weeks, followed by every 2 weeks until the 12th week and every 4 weeks until the 24th week. The primary outcome was 50% or more reduction in VAS score measured at week 4 compared to baseline. The secondary outcome was improvement of quality of sleep evaluated by a 5-point questionnaire (very bad to very good) recorded at the same time frames. The maintenance of improved VAS scores beyond the first 4 weeks was also considered a secondary outcome. Significant VAS improvement was reported at 4 weeks and also over subsequent weeks (for the toxin

Table 4.1 Class III (controlled, but not blinded) studies suggesting efficacy of BoNT therapy in PHN

Author/ date	#pts	Type of toxin	Dose (units); site of injection	Assessment scale(s)	Frequency	Results
Ding et al. [26]	58	Type A Chinese toxin	50–100 SC	VAS, NPS, SF-36	First at 2 weeks, then every month for 6 months	VAS improved in 78% of patients along with significant improvement of NPS and SF-36 ($P < 0.05$)
Jain et al. [27][a]	19	Type A aboA	500, 25 u/site; SC	VAS	1, 2, 4, 8, and 16 weeks	Significant improvement of VAS ($P < 0.05$) in all assessments
Hu et al. [28]	13	Type A Chinese toxin	50–100, 4 u/site; SC	VAS	1, 2, 4, 6, 12, and 16 weeks	Initial VAS >9 for all patients. At week 8, VAS score was under 4 for all patients ($P < 0.05$)

VAS Visual analog scale, *NPS* Neuropathic pain scale, *SF-36* quality of life scale, *SC* subcutaneous, *aboA* abobotulinumtoxinA (Dysport)

[a]This study included two pregnant women; both had an uneventful pregnancy and delivered normal babies

group, $P < 0.001$). Patients receiving BoNT also demonstrated significant improvement in quality of sleep and reduction of sleep scores along the same timelines.

These data are supported by three Class III studies (controlled, but not blinded) recently published on the issue of BoNT therapy for PHN (Table 4.1).

In a meta-analysis study of 12 randomized clinical trials (RCTs) focusing on interventional therapy, botulinum toxin injection and radiofrequency pulse therapy were found to be the most effective modes of treatment for postherpetic neuralgia. BoNT therapy was superior to spinal cord stimulation at 2 weeks and 3 months [29].

In another meta-analysis of 7 RCTs including 725 patients, Li et al. [30] found treatment with botulinum toxin for postherpetic neuralgia decreased VAS scores significantly at 1 month ($P < 0.0001$), 2 months ($P < 0.0007$), and 3 months ($P < 0.0001$) post injection. The authors concluded that BoNT therapy in postherpetic neuralgia is effective and safe.

Case Report

A 62-year-old female was referred to the Yale Botulinum Toxin Treatment Clinic for evaluation of severe right retroauricular pain. The onset of pain was specified to 2 years ago by the patient. At the onset, the pain involved both inside and behind the right ear. A course of antibiotics was not helpful. A few weeks later, with the appearance of typical skin lesions, zoster infection was diagnosed and treated with

Acyclovir. The skin lesions gradually improved, but the right retroauricular pain continued and grew in intensity. Some of the bouts of pain ended in severe headaches. The pain was described as jabbing and stabbing resulting in loss of sleep and marked apprehension in anticipation of the next bout. A variety of analgesic medications including gabapentin, pregabalin, and oxycodone were not helpful. The pain was often scored as 10 of 10 on visual analog scale (VAS) and described as unbearable.

On examination, there was discoloration along with scars of zoster infection behind the right ear. A total of 60 units of onaA toxin was injected in a grid-like pattern behind the left ear subcutaneously at 20 points (3 units/point) using a 30-guage needle (Fig. 4.2). The dilution was 100 units per 2 cc of saline. Patient reported a sharp drop in pain frequency and intensity (VAS down from 10 to 3) 5 days after the injections. The pain then disappeared at week 2 postinjection and

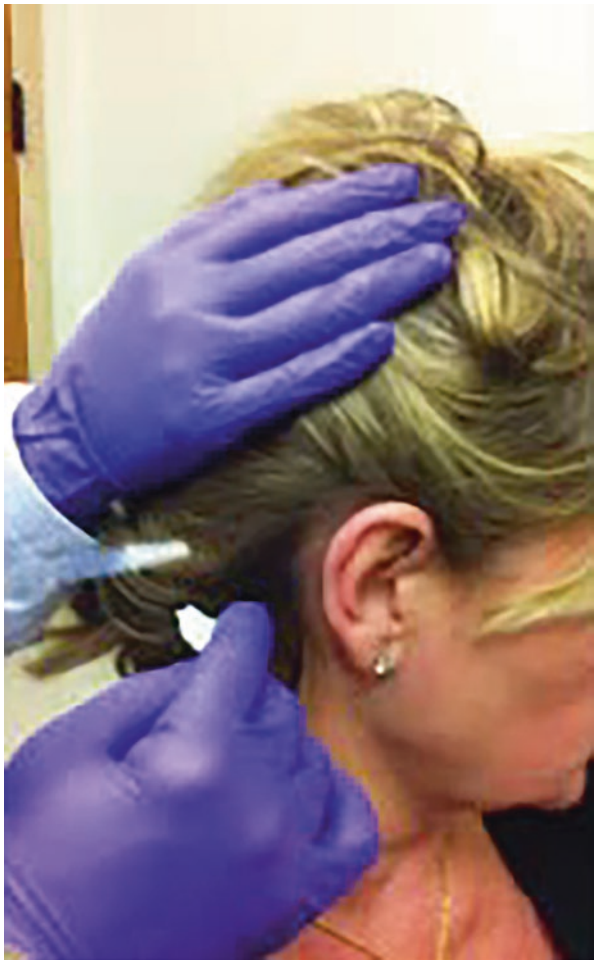

Fig. 4.2 The scheme of injection in the case presented above with herpetic involvement of skin behind the right ear

gradually reappeared at 2.5 months. Over the next 2 years, the patient received similar injections every 3 months. Each treatment resulted in significant reduction in pain. The last injection lasted 6 months with the returning pain reported as subtle (1 in VAS scale). The patient described no side effects. In an interview 2 years after treatment, the patient was very pleased with the outcome.

Comment

The author has treated six patients with PHN with subcutaneous injections of onaA. The dose ranged from 60 to 200 units based on the extent of the involved skin. The treatment was very effective in five patients (example, Case 1). In one patient with very extensive zoster infection of the chest wall, however, treatments with onaA (twice) similar doses failed to alleviate the pain.

Based on the above-mentioned two class I studies, BoNT-A treatment possesses level A efficacy (effective) for treatment of PHN [34]. The role of other BoNTs needs to be investigated. Failure of some patients with PHN to respond to onaA may be related to extensive pathology possibly extending to pain pathways in CNS or possibly requiring higher doses.

The Effect of Botulinum Toxin on Itch Associated with PHN

In 2008, Salardini et al. [31] first reported significant improvement of a recalcitrant itch with local onabotulinumtoxinA injection in a patient who had developed severe pruritus (itching) at the site of frontal sinus surgery. Since then and based on additional reports, local injection of BoNT-A is considered as a therapeutic option for chronic pruritus in dermatology [32]. Recently, Gharib et al. [33] reported marked improvement of pruritus associated with PHN after injection of onabotulinumtoxinA in four patients. The toxin was injected into the dermis, 2.5–5 units/site, 2 cm apart.

Posttraumatic Neuralgia

Pathophysiology Peripheral trauma triggers a cascade of events which involve nociceptor receptor sites, peripheral nerve endings, dorsal root ganglia (DRGs), spinal cord neurons, and central sensory neurons. Damaged nerve endings often accumulate pain mediators (glutamate, substance P) and new sprouts from the nerve endings demonstrate increased density of sodium channels [35] which increase peripheral nociceptive firing and generate ectopic discharges. New sprouts show increased sensitivity to cytokines, prostaglandin, and catecholamines. This periph-

eral sensitization increases the volume of nociceptive volleys which enter dorsal root ganglia and the spinal cord increasing neural excitement and leading to neuropathic pain..

Histologic changes which develop after peripheral trauma in DRG and spinal cord indicate increased neural excitation. In DRG, there is overgrowth of sympathetic nerves and abnormal linkage of A and C fibers [36]. In the spinal cord, dark cells appear in dorsal horns which presumably represent dying inhibitory neurons of glycinergic and gabaergic types [37, 38]. Demise of inhibitory neurons leads to enhanced excitation of central neurons. It has also been shown that after peripheral nerve injury, many large alpha/beta afferents (usually ending in Rexed lamina III) grow and penetrate more superficial levels (Rexed lamina II and I of dorsal horn) and gain access to low threshold pain afferents [39].

Treatment

The pain after peripheral nerve injury has the character of neuropathic pain and is characterized by local burning sensation and hyperalgesia. In general, medical treatment of posttraumatic neuralgia utilizes administration of analgesic agents as listed above in Table 5.2 for postherpetic neuralgia. Additional treatments for persistent PTN include nerve block by single injection or infusion, transcutaneous electrical nerve stimulation (TENS), and transcutaneous magnetic stimulation of peripheral nerves as well as spinal cord (dorsal horn) stimulation which leads to increased GABA release. In some cases, surgery may be necessary for removing a posttraumatic local neuroma.

BoNT Treatment of Posttraumatic Neuralgia

(A) Posttraumatic Neuralgia Secondary to Peripheral Trauma

Two placebo-controlled and double-blind studies have provided information on the efficacy of BoNT therapy in posttraumatic neuralgia.

Ranoux et al. [40] screened 61 consecutive patients of whom 29 met the criteria of neuropathic pain and eligibility for BoNT treatment. These patients were enrolled in a randomized, prospective double-blind study that investigated the efficacy of onaA in neuropathic pain. Nineteen patients were women. Twenty-five patients had posttraumatic neuralgia, and four patients had postherpetic neuralgia. In the posttraumatic group,18 patients had surgical trauma and seven nonsurgical trauma to single nerves. The primary outcome was self-reported level of pain in past 24 h on an 11-point scale of brief pain inventory (0–10) from a diary. Pain level was assessed at baseline and at 4 and 12 weeks postinjection. Secondary outcomes included degrees of brush allodynia, mechanical sensation and pain threshold, thermal

sensations and pain threshold, as well as neuropathic pain symptom inventory; all were assessed at aforementioned time points.

A neurologist, not involved in the study, administered the BoNT-A (onaA) solution intradermally at points 1.5 cm apart. The dilution was 100 units in 4 cc of preservative-free saline. The mean number of injection sites was 20 +/− 8.3. The dose ranged from 20 to 190 units.

The pain intensity started to decrease from week 2 ($P = 0.02$) in favor of onaA and remained improved until week 14 ($P = 0.03$). The average pain intensity assessed at each visit improved in the toxin group (0.007). Allodynia to brush also improved significantly, and pain threshold to cold was decreased in the BoNT group. Injections were painful, but no patient reported any side effects.

Attal et al. [41] assessed efficacy of repeated BoNT injections in 64 patients (34 in BoNT group, 32 in saline group) with neuropathic pain in a double-blind, placebo-controlled study that was conducted at three centers. Twenty-five patients who received BoNT (74%) injections had posttraumatic neuralgia. Patients had two injections, 12 weeks apart. The selected toxin for the study was onabotulinumtoxinA (onA/Botox). Injections were done 1.5 to 2 cm apart, 5 units per site. Depending on the extent of the involved skin, up to 300 units were injected (mean total dose of injection for the first injection was 199 units and the for the second injection was 176.8 units). The patient's response was evaluated at 4, 6, 12, 16, and 24 weeks after the first injection. The primary outcome was the efficacy of two successive injections of onaA compared to placebo measured as mean pain intensity in visual analogue scale (VAS) of 0–10. The secondary outcomes were safety and tolerability during the study period and the therapeutic gain in terms of relief of spontaneous pain as well as a number of other measures (neuropathic pain symptom inventory, local hyperesthesia, etc.). Compared to placebo, self-reported pain intensity was significantly decreased after week 1 following each of the two injections and continued to be significantly decreased in each of the successive weeks during the duration of the study (Ps ranging from 0.013 to 0.0001) (Fig. 4.3). A number of secondary outcomes also showed significant improvement such as patients' global impression of change (PGIC). Side effects were limited to pain at the site of injection, and it did not differ between toxin and placebo.

The following case of BoNT therapy in posttraumatic neuralgia is presented from the author's experience.

Case Report

A 56-year-old woman was referred to the Yale Movement Disorder Clinic for evaluation of severe posttraumatic neuralgia and to be considered for BoNT treatment. Twelve years earlier, her car was forcefully rear-ended when she braked hard in order to avoid hitting a car in front of her. The accident heavily bruised her right ankle and the lateral aspect of her right foot. The foot and ankle continued to ache, and an area of intense allodynia developed over the lateral malleolus extending up

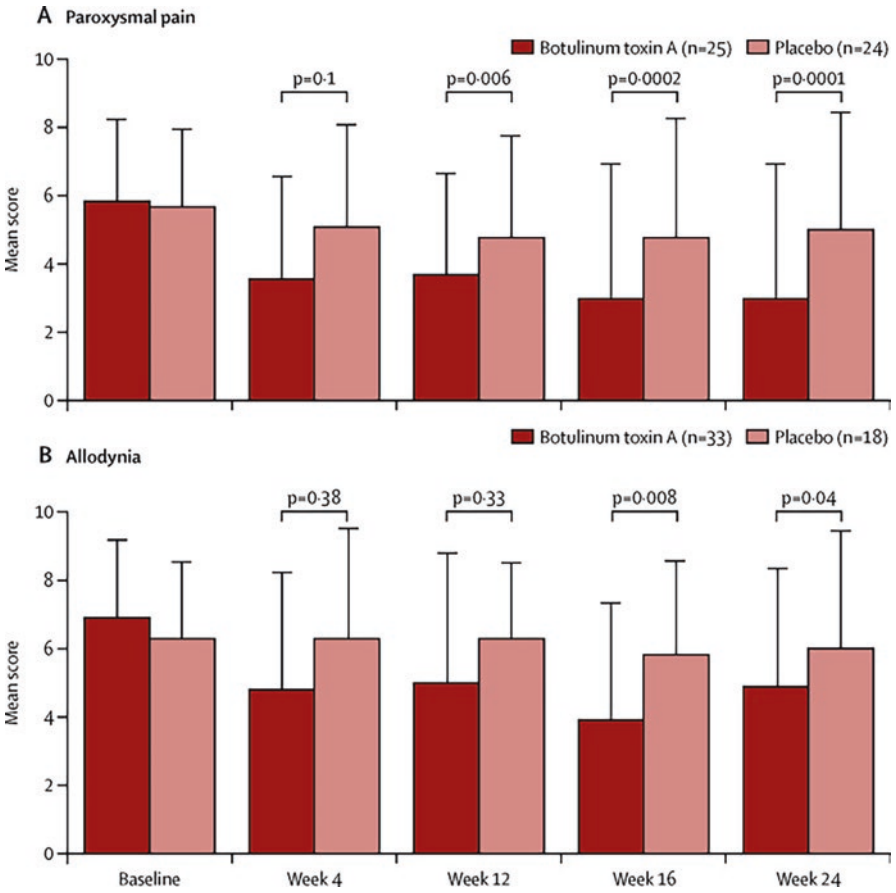

Fig. 4.3 Significant response of pain paroxysms and allodynia to BoNT-A treatment in a cohort with posttraumatic pain. (From Attal et al., Lancet 2016. Reproduced with permission from Publisher (Elsevier))

to the lower leg. A large number of medications failed to improve either the pain or the local allodynia. The most recent medications included gabapentin, pregabalin, tramadol, capsaicin ointment, and voltaren gel. In the patient's own words: "The physical, emotional and psychological impact of my chronic pain defies description. Everynight, I have to take tylenol, advil, ambien, apply ankle soak, topical pain cream and heat wrap in order to be able to sleep. With all this, many nights I am unable to sleep due to persistent pain. Even the pressure of sheets, would cause the pain to flare up – sleeping on my side is impossible."

On examination, muscle strength was normal, but foot movements were slow and intensified the ankle pain. A large area of allodynia and hyperesthesia was present including the lateral aspect of the right foot extending 10 cm above the right ankle. The most intense allodynic region was over the lateral malleolus extending to 5 cm above (Figs. 4.4 and 4.5).

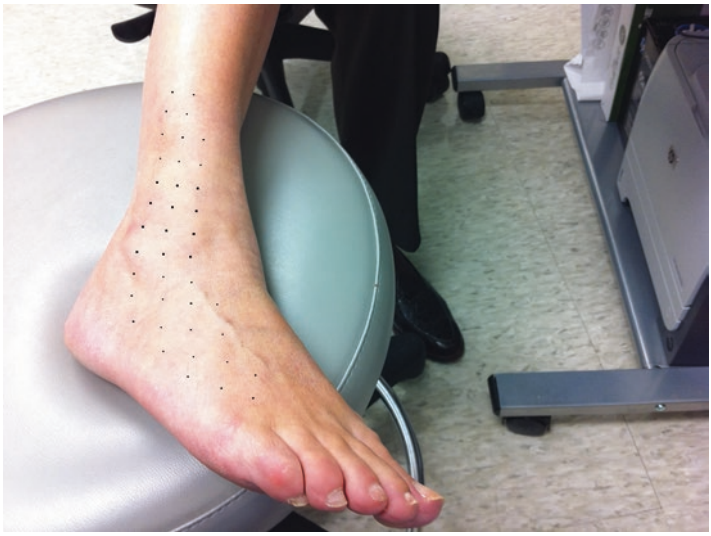

Fig. 4.4 Sites of subcutaneous injections. Darker dots represent the areas of maximum pain and tenderness

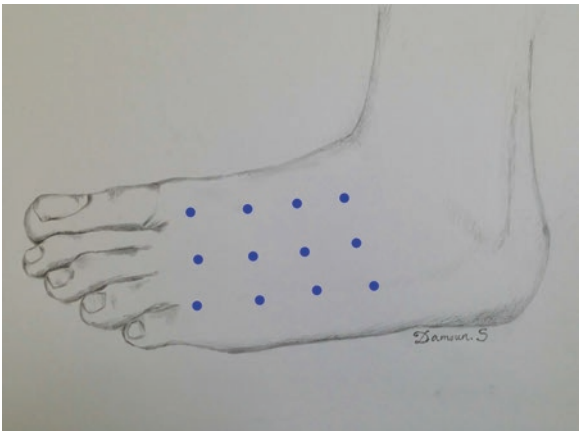

Fig. 4.5 Suggested sites of injection (subcutaneous) in painful diabetic neuropathy. Drawing courtesy of Damoun Safarpour, MD

OnabotulinumtoxinA (onaA) was injected subcutaneously into the dorsolateral aspect of the right foot (50 units; 20 sites—grid pattern) including the region of lateral malleolus (Fig. 4.4). The patient reported 30% reduction of pain (VAS score went down to 7 from 10) a week after the first injection and 90% decrease after the second injection (VAS score went down to 1–2) 6 months later. The patient noted: "the effect after the second injection was astounding. I stopped taking gabapentin and using pain wrap at night. I can now wear high heal shoes and clothes that rub against my ankle. I am looking forward to wearing boots for the first time in

12 years!". An examination 3 months after the second injection showed marked reduction of allodynia which was now much less intense and limited to only a small area above the lateral malleolus.

(B) **Posttraumatic Neuralgia Secondary to Spinal Cord Injury**

Central posttraumatic neuralgia is caused by trauma to the central nervous system, and in most cases, the site of trauma is the spinal cord.

Han et al. [42] investigated the effect of BoNT injection in 40 patients who suffered from chronic neuropathic pain following spinal cord injury. The study was double-blind and placebo-controlled assessing the effect of subcutaneous injection of 200 units of onabotulinumtoxinA (Meditoxin, South Korea) delivered in a checkerboard pattern into the region of pain. Patients were evaluated with VAS, short-form McGill pain questionnaire and the Korean version of World Health Organization quality of life questionnaire (WHOQOL-BREF). Evaluations were performed before BoNT injection and at weeks 4 and 8 after the injection. At 4 and 8 weeks after injection, the VAS score (primary outcome) for pain was reduced by 18.6 and 21.3 mm, respectively, for onaA group compared to 2.6 and 0.3 mm reduction, respectively, noted for the placebo group. The comparative values for both 4 and 8 weeks were statistically significant in favor of onaA ($P = 0.0027$ and $P = 0.0057$). Among secondary outcomes, the Korean version of SF-MPQ showed significant reduction of the total score ($P = 0.0008$) as well as significant reduction of sensory and affective scores in the onaA group. Among the responders in the onaA group, 55% and 45% reported pain relief of 20% or greater at 4 and 8 weeks compared to 15% and 10% in the placebo group. Improvements in the score for the physical health domain of the WHOQOL-BREF in the BoNT-A group showed a trend toward significance ($P = 0.0521$) 4 weeks after the injection. No motor or sensory deficit was noted after BoNT injections.

Recently, Chun et al. [43] in a double-blind cross-over study tested the efficacy of BoNT-A against placebo in 8 patients with spinal cord (SC) injury at T10–L3 level and persistent posttraumatic neuralgia. Patients received a total dose of 200 units of onabotulinumtoxinA injected subcutaneously in a grid-like pattern into several sites, 1 cm apart from each other. Although the pain intensity results (measured by VAS) did not reach the level of statistical significance (probably due to the small number of patients), the percentage of patients that demonstrated improvement of the average pain intensity from baseline (weeks 8 and 12) was considerably higher in the BoNT group compared to the placebo group (33% vs. 0%). Additionally, at 2 and 4 weeks post-BoNT-A injection, almost all participants reported some degree of reduced pain, while the same was not observed postplacebo injection (83% vs. 0%).

The above-mentioned human observations on the analgesic effect of BoNT therapy for PTN in SC injured human are supported also in animal models of spinal cord injury with posttraumatic neuralgia and allodynia [44, 45].

Comment The level of evidence for efficacy of onaA for PTN after peripheral nerve injury is A (effective) based on the above-mentioned two class I studies. The

case presented above is an example of PTN with severe allodynia showing a remarkable response to onaA after two treatments. Similar more significant responses after the second or third injection with onaA have also been reported for chronic migraine (see Chap. 5). A number of patients with PTN may later develop complex regional pain syndrome (CRPS), a condition which is more difficult to treat. An important remaining question is whether or not early treatment of PTN with onaA may prevent development of CRPS in some patients. The level of evidence for efficacy of onabotulinumtoxinA in posttraumatic neuralgia caused by spinal cord injury is B (probably effective), based on the availability of one class I study [42].

Metabolic and Drug-Induced Painful Peripheral Neuropathies

A large number of metabolic derangements and medications affect the peripheral nerves. In some, pain is a major symptom. Total coverage of all painful metabolic neuropathies is beyond the scope of this chapter. The focus of this section is on painful diabetic neuropathy, the only metabolic neuropathy for which blinded, placebo-controlled clinical trial results with BoNT treatment are available. No blinded data on BoNT treatment of drug-induced peripheral neuropathies is available; however, because of its importance and frequency, neuropathic pain related to chemotherapy is briefly discussed with a representative case report from the author's experience with onaA.

Diabetic Neuropathy

Among metabolic disorders, diabetic neuropathy (DN) can be considered a model of metabolic neuropathic pain. Painful neuropathy is more common in type 2 diabetes with prevalence of 25–26% [46] versus the 16% reported for type 1 diabetes among the younger individuals [47]. The persistent pain often has a burning and aching quality. Examination shows reduced or lost sensory modalities consistent with DN as well as areas of hyperesthesia and allodynia. Chronic pain causes anxiety and depression impairing the quality of life due to psychosocial distress and disrupted sleep.

Pathophysiology

For years, hyperglycemia was considered the main reason for development of pain in DPN. Recent data suggests hypoinsulinism and abnormal insulin signaling as important contributing factors as well [48]. At the molecular level, sodium channels, nonselective calcium channels linked to transient receptor potential receptor (TRP)

and receptors for nerve growth factors (Trks) are all expressed highly in DRG neurons and believed to have a role in the pain of diabetic neuropathy. More recently, CaV3.2 T-type voltage-gated calcium channels (T-channels) have been identified as key players in the sensitized (hyperexcitable) state of nociceptive sensory neurons (nociceptors) in response to hyperglycemia and suggested as important players in painful symptoms of diabetic neuropathy [49]. The role of different sodium channels in pathophysiology of PDN is currently being explored.

Treatment of Painful Diabetic Neuropathy (PDN)

The treatment strategy for PDN focuses on controlling hyperglycemia and the use of known drugs for neuropathic pain. However, a recent comprehensive review of the subject of painful and nonpainful diabetic neuropathies noted that less than one-seventh of patients with PDN express sufficient pain relief from current medications [50]. Recently, new modalities of treatment have been introduced in this area based on a phenotypic profiling approach. For instance, carbamazepine may correct the hyperexcitability caused by a sodium channel Nav1.8 mutation in a patient with PDN [51]. Moreover, it has been shown in one double-blind, placebo-controlled study that lacosamide a Nav1.7 and Nav1.8 sodium channel blocker significantly reduces pain in patients with Nav1.7 SFN [52].

BoNT Treatment in Diabetic Neuropathy

Five double-blind, placebo-controlled studies have investigated the efficacy of onaA in painful diabetic neuropathy. The design of these studies, study class, type and dose of toxins used, outcome measures, and results are shown in Table 4.2. The technique of injection per Yuan et al. [53] is presented in Fig. 4.5.

Comment

The studies cited in Table 4.2 show significant improvement of pain, sleep quality, tactile, and mechanical hyperesthesia in patients with PDN following subcutaneous or intradermal injection of BoNTs in the involved feet. Both onaA and aboA have been shown to be efficacious. Side effects were minimal and mainly confined to pain at the site of injection. Since all studies despite being double-blind and placebo-controlled are class II, in the absence of class I studies, the level of efficacy of BoNT in PDN is defined as “probably effective “using AAN guidelines [4, 5]. There is a need for conducting multicenter class I studies in this area.

Table 4.2 Double-blind placebo-controlled studies assessing the efficacy of BoNTs in PDN

Authors and year	Study class design	# patients	Toxin	Total dose/ units/ injection site	Mode and site of injection	Assessment scale(s)	Results
Yuan et al. [53]	II, CO	20	onaA	48/foot	Intradermal, 4 units/site, 12 sites (Figs. 4.4, 4.5 and 4.6)	VAS PSQI (Chinese version); quality of life (SF32)	VAS score reduced at weeks 1, 4, 8, and 12 ($P < 0.05$); sleep improved 1 week after onaA injection ($P < 0.05$); quality of life also improved more in onA group (P value not significant)
Chen et al. [54]	II, CO	18	onaA	48/foot	Intradermal, 4 units/site, 12 sites	Tactile threshold; mechanical pain using weight strings	Tactile perception and mechanical pain were decreased markedly at weeks 1, 4, 8, and 12 after onaA injection ($P < 0.05$)
Ghasemi et al. [55]	II, PD	20	aboA	96–120/ foot	8–10 units/ site, 12 sites	VAS; NPS	NPS: Reduced intensity ($P < 0.001$); VAS: 30% no pain ($P = 0.01$).
Restivo et al. [56]	II, PD	50	onaA	100 & 30/foot	Into GC muscle or small foot flexors	VAS; cramp frequency; cramp interference with daily life	All measures improved significantly over 12 weeks
Salehi et al. [57]	II, PD	32	aboA	100/foot	12 sites using a grid pattern	VAS; PSQI; NPS	Significant improvement of VAS, PQSI, and NPS over 12 weeks ($P < 0.0001$)
Taheri et al. [58]	II, PD	141	aboA	150/foot	12 sites	VAS; sharp and hot sensations	All reduced significantly ($P < 0.05$)

CO Cross over design, *PD* Parallel design, *VAS* Visual analogue scale, *onaA* onabotulinumtoxinA (botox), *aboA* AbobotulinumtoxinA (dysport), *NPS* Neuropathic pain scale, *PSQI* Pittsburg sleep quality index, *GC* Gastrocnemius

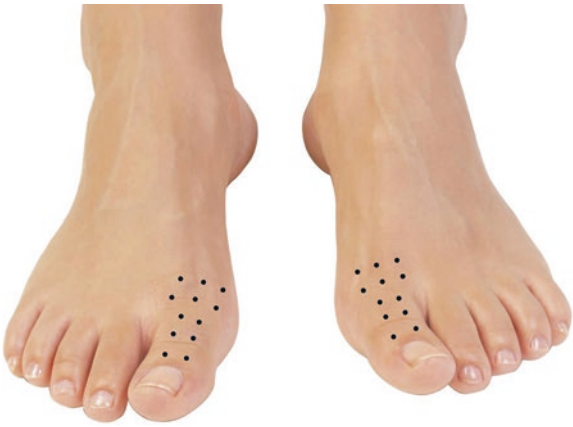

Fig. 4.6 Sites of BoNT injection in patient with chemotherapy-induced peripheral neuropathy

Painful Neuropathy Related to Drugs and Chemotherapeutic Agents

There are no controlled studies assessing the efficacy of BoNTs in drug-induced and chemotherapy-related painful neuropathies. The case below describes author's experience with one of the two patients in whom treatment with onaA resulted in marked improvement of pain associated with chemotherapy-induced allodynia .

Case Report

A 64-year-old man was referred to the Yale Botulinum Toxin Treatment Clinic for evaluation of severe burning pain in both feet. One year earlier, he had been diagnosed as having a myelodysplastic syndrome for which he had received stem cell transplant. The pain began a month after the transplant while he was receiving immune system modifying agents (tacrolimus, cellcept, and prednisone). The pain first involved both upper and lower limbs equally, but intensified in the feet over the succeeding months. He described the pain as frequent "electrical shocks" or "like a swarm of bees stinging you all at once." The most intense pain affected dorsal and ventral aspects of the big toe and the adjacent dorsum of the foot bilaterally. The pain worsened at night and was described as "excruciating." The patient rated his pain in VAS as 10 out of 10. Treatment with a variety of analgesic medications including duloxetine, gabapentin, methadone, and oxycodone provided only minimal relief.

Neurological examination showed decreased light touch, pin-prick and vibration sense in the distal part of all extremities, and absent ankle jerks. There was exquisite sensitivity to light touch in the dorsum and ventral aspects of the big toes as well as a small area on the dorsum of both feet close to the big toes which resulted in

Fig. 4.7 Ambroise Pare from Science Photo Gallery

intense pain (severe allodynia) upon palpation. Each of these three areas, in each foot, was injected with 10 units of onaA subcutaneously. Six to eight sites were injected per area (1.5–2 units/site) for a total of 30 units per foot (Figs. 4.4, 4.5, 4.6 and 4.7). Within 2 weeks after this treatment, the patient noted marked improvement. In evaluations performed at 4 and 8 weeks after treatment, the patient reported his level of pain as 2 out of 10 "very low" in VAS. He expressed his level of satisfaction in PGIC (patient global impression of change) as very satisfactory.

Comment

Painful neuropathy related to chemotherapeutic agents is a major issue in clinical oncology. If controlled trials can demonstrate efficacy of BoNTs in alleviating this form of neuropathic pain, it would be very beneficial to these patients who are often on multiple medications and not enthusiastic about taking additional pain medications.

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is described as a medical condition characterized by chronic pain (usually beginning in one limb and more often in the foot) after tissue injury (neural or nonneural) involving regional rather than nerve distribution. For reasons that are only poorly understood, a traumatized limb affected by somatic pain gradually develops additional autonomic and trophic dysfunction. CRPS is usually diagnosed by the criteria set forth by the International Pain Study Society (IPSS) first published in 1994 and then (the revised edition) in 2003 Budapest criteria (Table 4.3) [59].

Some historians traced the first description of a condition similar to CRPS to Ambroise Pare (Fig. 4.7), a sixteenth-century physician/surgeon, who described a condition akin to CRPS characterized by chronic pain and trophic changes after iatrogenic injury to the limb that had developed in Charles IX, his sovereign [60]. Weir Mitchell's description of causalgia among soldiers who had nerve injury during the American Civil War now fits the description of CRPS II, whereas in CRPS I (previously called sympathetic dystrophy), the preceding trauma does not cause nerve injury. Pain in both kinds of CRPS has a burning and jabbing quality, and the involved limb has areas of allodynia and hyperesthesia. Autonomic dysfunctions can be in the form of coldness or warmth of the limb with hyper- or hypohydrosis. Trophic changes include skin atrophy, hair loss, and nail changes [61]. Motor symptoms such as finger, hand, and arm dystonia and tremor may develop and cause further discomfort. Symptoms may progress proximally and result in pain and dystonia of the arm and shoulder muscles. In severe cases, loss of vascular supply threatens development of gangrene and may necessitate even limb amputation.

Table 4.3 Budapest clinical diagnostic criteria for CRPS [59]

1. Continuing pain, which is disproportionate to any inciting event.
2. Must report at least one symptom in *three of the four* following categories:
   - *Sensory:* Reports of hyperesthesia and/or allodynia.
   - *Vasomotor:* Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry.
   - *Sudomotor/edema:* Reports of edema and/or sweating changes and/or sweating asymmetry.
   - *Motor/trophic:* Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, and dystonia) and/or trophic changes (hair, nail, and skin).
3. Must display at least one sign at time of evaluation in *two or more* of the following categories:
   - *Sensory:* Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement).
   - *Vasomotor:* Evidence of temperature asymmetry and/or skin color changes and/or asymmetry.
   - *Sudomotor/edema:* Evidence of edema and/or sweating changes and/or sweating asymmetry.
   - *Motor/trophic:* Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, and dystonia) and/or trophic changes (hair, nail, and skin).
4. There is no other diagnosis that better explains the signs and symptoms.

Between 2% and 5% of patients with peripheral injury develop CRPS with age of 42 years being the average age of onset [62]. In the Olmstead county (Minnesota) study, the prevalence of CRPS was cited as 8.57 and 2.16/100,000 for females and males, respectively [63], whereas in a more recent study from Denmark, higher figures of 40.4 and 11.9 were reported for females and males, respectively [64]. Schwartzman described the natural history and evolution of symptoms in CRPS in 656 patients through a questionnaire [65]. All patients had CRPS for more than 1 year and were followed for many years (38 patients for over 20 years). In his experience, CRPS was 4 times more common in women. The most common cause of injury was motor vehicle accident (23.26%) followed by falls (14.6%). In 10%, a surgical procedure preceded the symptoms. The severity of touch allodynia and mechano-allodynia in CRPS has increased significantly over the years ($P < 0.05$). Thirty-one percent of the patients reported pain spread to the areas contiguous with the site of initial injury, and 10% to 11% had spread either to the same contralateral limb (mirror pattern), ipsilateral other limb (hand–foot), or contralateral nonmirrored limb (right hand, left foot). Medications helped in 50% of cases, but only 5% responded to meditation, acupuncture, biofeedback, or dorsal column stimulation. In 15% of the patients, nothing helped. Close to 75% of the patients required narcotics for pain relief. Cold weather and physical activity were the two main factors that aggravated the pain (48.2% and 37%, respectively). Skin color changes and temperature changes increased significantly from the first 5 to 15 days of illness (from 71% and 83% to 81% and 95%, respectively). Local swelling also increased from year 1 (75%) to year 15 (90%) ($P = 0.024$). At year 1, 93% and at year 15, 94% reported loss of strength in the involved limb. Abnormal limb posture was noted in 57% of the patients at year 1 and in 80% of the patients at year 10 ($P = 0.018$). There was an increase in spontaneous falls from 27% at year 1 to 35% at year 10 of the illness. With advanced disease, 71.9% of the patients reported difficulty in sleeping and 68.5% reported tiredness. In 81% of the patients, pain was so severe that they had to stop working. Pain affected general activity, mood, and enjoyment of life in 97% of the patients. None of the patients demonstrated spontaneous remission. The pain was refractory and only modestly responded to medications. More than half of the patients demonstrated cognitive difficulties which is consistent with what has been reported in chronic pain patients. Powerful analgesic medications used by many of these patients may account for some of the cognitive difficulties observed in patients with chronic CRPS.

Pathophysiology

For years, primary dysfunction of the sympathetic nervous system was held responsible for the development of CRPS. This view is now modified in favor of neuroinflammation and deranged autoimmunity with small C fiber damage playing a pivotal role. Damage to C-fibers could lead to neurogenic inflammation, ectopic firing, vasodilation (via axon reflex), and/or hypoxic/ischemic injury [66, 67]. There is

evidence that, in some patients, neural inflammation extends to the spinal cord. In one patient with longstanding CRPS, tissue examination of the dorsal horn demonstrated significant activation of microglia and astrocytes with neuronal loss [68].

Treatment of Complex Regional Pain Syndrome

Treatment of CRPS is difficult and geared to relief of pain and modification of the course of the disease. It would appear that suppression of pain early during the course of the disease is important since patients who have a lot of pain during the initial injury are destined to have a more severe form of CRPS I [69]. It is generally agreed that physical therapy offers some help and is recommended to be applied early during the course of disease [70]. Treatment of pain with tricyclic antidepressants, calcium channel blockers including gabapentin and pregabalin, serotonin/norepinephrine reuptake inhibitors, and locally delivered anesthetics is partially effective. Intranasal calcitonin (100–400 units) may relieve pain in some patients. The role of steroids in treatment of CRPS is controversial.

Sympathectomy has long been practiced for treatment of patients with severe CRPS [71]. Anhidrosis and Horner's syndrome are common complications of sympathectomy. Spinal cord stimulation is effective in a small number of patients. In a blinded study, intravenous infusion of ketamine (NMDA antagonist) effectively reduced pain in 16 of 20 patients with follow up of 6 months [72]. However, the recommended dose of 100 mg infused for 4 h/day for 10 days can be associated with significant hepatotoxicity requiring close liver function monitoring. Recently, a small double-blind, cross-over study of 12 patients has suggested the efficacy of intravenous immunoglobulin (IVIG) in CRPS [73]. In a retrospective study, Aradillas et al. [74] reported a mean 64% decrease in pain when 33 patients with severe CPRS were treated with plasma exchange ($P < 0.01$). A satisfactory level of pain control was maintained in 15 patients with weekly plasma exchange therapy.

BoNT Treatment of CRPS

The role of BoNTs in treatment of CRPS has been investigated both as an analgesic agent via subcutaneous and intramuscular injection and as an agent to induce analgesia via chemical sympathectomy. Argoff [75] reported alleviation of pain, improvement of skin color, and local edema in 11 patients with CRPS following intramuscular injection of onaA. Over the past 15 years, several case reports and retrospective observations have reported improvement of pain in CRPS following subcutaneous and intramuscular injections of BoNTs [76–79]. In contrast to these observations, a small double-blind study found no statistically significant difference between subcutaneous injections of onaA and placebo in 8 patients with severe CPRS allodynia [80]. Several studies have reported improvement of the symptoms

of CRPS after injection of BoNT-A or -B into the sympathetic ganglion [81–84]. In the largest study using this approach [84], investigators compared blindly the effect of 75 units of BoNT-A (onaA) with anesthetics in 48 patients (24 in each group). The authors found the group that was injected with BoNT-A demonstrated higher change in skin temperature compared with the control group which was maintained at 3 months (1.0 °C ± 1.3 vs. 0.1 °C ± 0.8, respectively; difference: 0.9 °C [95% CI, 0.3 to 1.5]; $P = 0.006$). Furthermore, pain intensity was significantly reduced in the botulinum toxin group compared with the control group at 1 month (−2.2 ± 1.0 vs. -1.0 ± 1.6, respectively; $P = 0.003$) and 3 months (−2.0 ± 1.0 vs. -0.6 ± 1.6, respectively; $P = 0.003$). BoNT injections into the lumbar sympathetic ganglion caused no significant side effect.

Comment

The natural history of CPRS reflects a debilitating condition with poor prognosis. One long-term follow-up study found little improvement of symptoms with current methods of treatment [72]. Although data regarding BoNT therapy in CRPS from retrospective case series are encouraging, so far, blinded data in a sizeable number of patients are only available in studies that conducted lumbar chemical sympathectomy with BoNTs. These studies, although positive, did not use placebo but compared the effect of BoNT injection into sympathetic ganglia with anesthetic agents. Clarification of efficacy of BoNT by limb injections in CPRS requires blinded study of large cohorts; in case of sympathetic blocks, blinded studies are needed that compare the effect of BoNT-induced chemical sympathectomy with placebo injections.

Residual Limb Pain and Phantom Pain

With increasing frequency of military conflicts, pain associated with loss of limb has become a major medical management issue among soldiers. It is predicted that in the United States, the number of patients affected by this type of pain will exceed three million by the year 2050 [85]. Pain associated with loss of limb can be a pain in the stump (residual limb pain: RLP) or felt in the region of the lost limb (phantom limb pain: PLP). The reported incidence of RLP after amputation is 22% to 43% and for PLP is 66% [86, 87]. The possible mechanism and pathophysiology of phantom pain are discussed in detail several recent reviews [89, 90, 91].

Pharmacological Treatment

Avilar et al. in a recent Cochrane review of the literature [91] concluded that for treatment of phantom pain "the short- and long-term effectiveness of opioids, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, and local anesthetics for clinically relevant outcomes including pain, function, mood, sleep, quality of life, treatment satisfaction, and adverse events remain unclear." The N-methyl D-aspartate (NMDA) receptor antagonists ketamine (versus placebo; versus calcitonin) and dextromethorphan (versus placebo), but not memantine, provided some analgesic effects. Memantine and amitriptyline failed to improve phantom pain. No data on long-term efficacy of the aforementioned agents in treatment of phantom pain are available.

BoNT Treatment of RLP and PLP

Two clinical observations, each performed on a small number of patients, have claimed that BoNT administration into stump muscles improves phantom pain. In one study [92], 4 patients were injected with 2500–5000 units of rimabotulinumtoxinB into the arm and leg stumps (two patients each). Injections were performed at multiple trigger points. All patients reported improvement in stump pain, PLP attacks, and improvement of local allodynia. One patient noted significant improvement of sleep. Improvements lasted for "many weeks." In one patient, a 12-month follow-up showed almost total pain relief. In another study [93], authors described significant improvement of phantom pain in 3 patients (two with accident injury and one with landmine injury) after EMG-guided administration of aboA (up to 500 units) into the stump muscles. All three patient reported level 3 (on a 0–3 scale) improvement on global clinical scale as well as substantial pain improvement on VAS. Pain improvement lasted 11 months. Patients were able to reduce their pain medications after BoNT treatment.

Unfortunately, these positive observations did not bear out in a recent prospective, parallel design, blinded study (Class III, no placebo) which compared the effect of onaA with that of combined lidocaine/methylprednisolone therapy [94]. In this study, investigators injected a total of 250–300 units of onaA or 10 mg depomedrol in 1% lidocaine in up to 6 tender points of 14 patients with RLP and PLP. There was no significant effect on phantom limb pain (PLP) from any of the two agents. Both agents, however, significantly improved RLP and pain tolerance. OnaA's effect on RLP and pain tolerability was stronger than that of lidocaine/depomedrol injection ($P = 0.002$ versus $P = 0.06$ and $P = 0.01$ versus 0.07, respectively). The relief of RLP in both groups lasted for 6 months.

Comment

Phantom pain is a fascinating area for BoNT research. Efficacy, if confirmed, would imply that peripheral administration of BoNT's can influence allodynia caused by central pain. The class III study cited above and open observations suggest efficacy of onaA for RLP. At this time, the level of efficacy of BoNT is U (undetermined) for both RLP and PLP due to lack of class I or II studies (using AAN's efficacy criteria) [4, 5].

Chapter Conclusion

Neuropathic pain is one of most common forms of human pain. Failure of response to current analgesic medications is not uncommon. The data on type A botulinum toxin (mostly onaA) is encouraging and indicate efficacy or probable efficacy in three major and common forms of neuropathic pain, namely, postherpetic neuralgia, posttraumatic neuralgia, and painful diabetic neuropathy. Controlled and placebo-controlled trials are necessary to assess the efficacy of BoNTs in other painful metabolic and drug-induced neuropathies, complex regional pain syndrome, residual limb pain, and phantom pain. Much remains to be learned about the most effective technique of injection, most effective dose, optimum dilutions, and differences among BoNTs in treatment of neuropathic pain.

References

1. Treede RD. Chapter 2: Peripheral and central mechanisms of neuropathic pain. In: Simpson, Mc Arthur, Dworkin, editors. Neuropathic pain –mechanisms, diagnosis and treatment. Oxford Publisher; 2012. p. 14–24.
2. Aoki RK, Francis J. Update on the nociceptive mechanism hypothesiss and relate disorders. Parkins and Relat Disord. 2011;17:S28–33.
3. Magrinelli F, Zanette G, Tamburin S. Neuropathic pain: diagnosis and treatment. Pract Neurol. 2013;13:292–307.
4. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008;71:1634–8.
5. 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.
6. Oaklander AL. The density of remaining nerve endings in human skin with and without postherpetic neuralgia after shingles. Pain. 2001;92:139–45.
7. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, Arbeit RD, Simberkoff MS, Gershon AA, Davis LE, Weinberg A, Boardman KD, Williams HM, Zhang JH, Peduzzi PN, Beisel CE, Morrison VA, Guatelli JC, Brooks PA, Kauffman CA, Pachucki CT, Neuzil KM, Betts RF, Wright PF, Griffin MR, Brunell P, Soto NE, Marques AR, Keay SK, Goodman RP, Cotton DJ, Gnann JW Jr, Loutit J, Holodniy M, Keitel WA, Crawford GE, Yeh SS, Lobo Z, Toney JF, Greenberg RN, Keller PM, Harbecke R, Hayward AR, Irwin MR,

Kyriakides TC, Chan CY, Chan IS, Wang WW, Annunziato PW, Silber JL. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352:2271–84.
8. Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley RJ. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. Clin Infect Dis. 1996;22:341–7.
9. Whitley RJ, Weiss H, Gnann JW Jr, Tyring S, Mertz GJ, Pappas PG, Schleupner CJ, Hayden F, Wolf J, Soong SJ. Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Ann Intern Med. 1996;125:376–83.
10. 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.
11. Thyregod HG, Rowbotham MC, Peters M, Possehn J, Berro M, Petersen KL. Natural history of pain following herpes zoster. Pain. 2007;128:148–56.
12. Baron R, Haendler G, Schulte H. Afferent large fiber polyneuropathy predicts the development of postherpetic neuralgia. Pain. 1997;73:231–8.
13. Park SY, Kim JY, Kwon JS, Jeon NY, Kim MC, Chong YP, Lee SO, Choi SH, Kim YS, Woo JH, Kim SH. Relationships of varicella zoster virus (VZV)-specific cell-mediated immunity and persistence of VZV DNA in saliva and the development of postherpetic neuralgia in patients with herpes zoster. J Med Virol. 2019;91(11):1995–2000. https://doi.org/10.1002/jmv.25543. Epub 2019 Jul 23. PMID: 31286531
14. Forbes HJ, Thomas SL, Smeeth L, Clayton T, Farmer R, Bhaskaran K, Langan SM. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. Pain. 2016;157(1):30–54. https://doi.org/10.1097/j.pain.0000000000000307. PMID: 26218719; PMCID: PMC4685754
15. Oster G, Harding G, Dukes E, Edelsberg J, Cleary PD. Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. J Pain. 2005;6:356–63.
16. Baron R, Tölle TR, Gockel U, Brosz M, Freynhagen R. A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: differences in demographic data and sensory symptoms. Pain. 2009;146(1–2):34–40. https://doi.org/10.1016/j.pain.2009.06.001. Epub 2009 Jul 9. PMID: 19592166. Barrett AM, Lucero MA, Le T, Robinson RL, Dworkin RH, Chappell
17. Cohen JI. Clinical practice: Herpes zoster. N Engl J Med. 2013;369:255–63.
18. Ghanavatian S, Wie CS, Low RS, Zhang N, Montoya JM, Dhaliwal GS, Swanson DL. Premedication with gabapentin significantly reduces the risk of postherpetic neuralgia in patients with neuropathy. Mayo Clin Proc. 2019;94(3):484–9. https://doi.org/10.1016/j.mayocp.2018.11.004. Epub 2019 Feb 2. PMID: 30718068
19. Werner RN, Nikkels AF, Marinović B, Schäfer M, Czarnecka-Operacz M, Agius AM, Bata-Csörgő Z, Breuer J, Girolomoni G, Gross GE, Langan S, Lapid-Gortzak R, Lesser TH, Pleyer U, Sellner J, Verjans GM, Wutzler P, Dressler C, Erdmann R, Rosumeck S, Nast A. European consensus-based (S2k) Guideline on the Management of Herpes Zoster – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 2: Treatment. J Eur Acad Dermatol Venereol. 2017;31(1):20–9. https://doi.org/10.1111/jdv.13957. Epub 2016 Nov 2. PMID: 27579792
20. Gross GE, Eisert L, Doerr HW, Fickenscher H, Knuf M, Maier P, Maschke M, Müller R, Pleyer U, Schäfer M, Sunderkötter C, Werner RN, Wutzler P, Nast A. S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia. J Dtsch Dermatol Ges. 2020;18(1):55–78. https://doi.org/10.1111/ddg.14013. Epub 2020 Jan 17. PMID: 31951098
21. Lee SH, Ryu KH, Kim PO, Lee HW, Cho EA, Ahn JH, Youn I, Yang KS. Efficacy of extracorporeal shockwave therapy in the treatment of postherpetic neuralgia: a pilot study. Medicine (Baltimore). 2020;99(12):e19516. https://doi.org/10.1097/MD.0000000000019516. PMID: 32195953; PMCID: PMC7220462

22. Sollie M, Thomsen JB, Sørensen JA. Autologous fat grafting seems to alleviate postherpetic neuralgia – a feasibility study investigating patient-reported levels of pain. J Plast Reconstr Aesthet Surg. 2021;74(2):350–6. https://doi.org/10.1016/j.bjps.2020.08.038. Epub 2020 Aug 21. PMID: 32917571
23. Texakalidis P, Tora MS, Boulis NM. Neurosurgeons' armamentarium for the management of refractory postherpetic neuralgia: a systematic literature review. Stereotact Funct Neurosurg. 2019;97(1):55–65. https://doi.org/10.1159/000499476. Epub 2019 Apr 17. PMID: 30995653
24. 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.
25. 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.
26. Ding XD, Zhong J, Liu YP, Chen HX. Botulinum as a toxin for treating post-herpetic neuralgia. Iran J Public Health. 2017;46(5):608–11. PMID: 28560190; PMCID: PMC5442272
27. Jain P, Jain M, Jain S. Subcutaneous injection of botulinum toxin in patients with post herpetic neuralgia. A preliminary study. J Assoc Physicians India. 2018;66(7):48–9. PMID: 31325262
28. Hu Y, Zou L, Qi X, Lu Y, Zhou X, Mao Z, Chen X, Liu K, Yang Y, Wu Z, Hu Y, Ma S. Subcutaneous botulinum toxin-A injection for treating postherpetic neuralgia. Dermatol Ther. 2020;33(1):e13181. https://doi.org/10.1111/dth.13181. Epub 2019 Dec 4. PMID: 31769900
29. Wen B, Wang Y, Zhang C, Xu W, Fu Z. Efficacy of different interventions for the treatment of postherpetic neuralgia: a Bayesian network meta-analysis. J Int Med Res. 2020;48(12):300060520977416. https://doi.org/10.1177/0300060520977416. PMID: 33317382; PMCID: PMC7739127
30. Li XL, Zeng X, Zeng S, He HP, Zeng Z, Peng LL, Chen LG. Botulinum toxin A treatment for post-herpetic neuralgia: a systematic review and meta-analysis. Exp Ther Med. 2020;19(2):1058–64. https://doi.org/10.3892/etm.2019.8301. Epub 2019 Dec 9. PMID: 32010269; PMCID: PMC6966161
31. Salardini A, Richardson D, Jabbari B. Relief of intractable pruritus after administration of botulinum toxin A (botox): a case report. Clin Neuropharmacol. 2008;31(5):303–6. https://doi.org/10.1097/WNF.0b013e3181672225. PMID: 18836352
32. McEwen MW, Fite EM, Yosipovitch G, Patel T. Drugs on the horizon for chronic pruritus. Dermatol Clin. 2018;36(3):335–44. https://doi.org/10.1016/j.det.2018.02.016. Epub 2018 Apr 26. PMID: 29929605
33. Gharib K, Mostafa A, Elsayed A. Evaluation of botulinum toxin type A injection in the treatment of localized chronic pruritus. J Clin Aesthet Dermatol. 2020;13(12):12–7. Epub 2020 Dec 1. PMID: 33488912; PMCID: PMC7819596
34. Brown EA, Schütz SG, Simpson DM. Botulinum toxin for neuropathic pain and spasticity: an overview. Pain Manag. 2014;4(2):129–51. https://doi.org/10.2217/pmt.13.75. PMID: 24641437
35. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009;9:723–44.
36. McLachlan EM, Jänig W, Devor M, Michaelis M. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. Nature. 1993;363:543–6.
37. Garrison CJ, Dougherty PM, Kajander KC, Carlton SM. Staining of glial fibrillary acidic protein (GFAP) in lumbar spinal cord increases following a sciatic nerve constriction injury. Brain Res. 1991;565:1–7.
38. Todd AJ, Sullivan AC. Light microscope study of the coexistence of GABA-like and glycine-like immunoreactivities in the spinal cord of the rat. J Comp Neurol. 1990;296:496–505.
39. Yaksh TL, Caplan SR. Physiology and pharmacology of neuropathic pain. Anesth Clin North Am. 1997;15:335–52.
40. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol. 2008;64:274–83.

41. Attal N, de Andrade DC, Adam F, Ranoux D, Teixeira MJ, Galhardoni R, Raicher I, Üçeyler N, Sommer C, Bouhassira D. Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2016;15(6):555–65. https://doi.org/10.1016/S1474-4422(16)00017-X. Epub 2016 Mar 2. PMID: 26947719
42. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type a for neuropathic pain in patients with spinal cord injury. Ann Neurol. 2016;79(4):569–78. https://doi.org/10.1002/ana.24605. Epub 2016 Feb 16. PMID: 26814620; PMCID: PMC4825405
43. Chun A, Levy I, Yang A, Delgado A, Tsai CY, Leung E, Taylor K, Kolakowsky-Hayner S, Huang V, Escalon M, Bryce TN. Treatment of at-level spinal cord injury pain with botulinum toxin A. Spinal Cord Ser Cases. 2019;5:77. https://doi.org/10.1038/s41394-019-0221-9. PMID: 31632735; PMCID: PMC6786298
44. Vacca V, Madaro L, De Angelis F, Proietti D, Cobianchi S, Orsini T, Puri PL, Luvisetto S, Pavone F, Marinelli S. Revealing the therapeutic potential of botulinum neurotoxin type A in counteracting paralysis and neuropathic pain in spinally injured mice. Toxins (Basel). 2020;12(8):491. https://doi.org/10.3390/toxins12080491. PMID: 32751937; PMCID: PMC7472120
45. Chun A, Levy I, Yang A, Delgado A, Tsai CY, Leung E, Taylor K, Kolakowsky-Hayner S, Huang V, Escalon M, Bryce TN. Treatment of at-level spinal cord injury pain with botulinum toxin A. Spinal Cord Ser Cases. 2019;5:77. https://doi.org/10.1038/s41394-019-0221-9. PMID: 31632735; PMCID: PMC6786298
46. Boulton AJ. Diabetic neuropathy: classification, measurement and treatment. Curr Opin Endocrinol Diabetes Obes. 2007;14:141–5.
47. Barrett AM, Lucero MA, Le T, Robinson RL, Dworkin RH, Chappell AS. Epidemiology, public health burden, and treatment of diabetic peripheral neuropathic pain: a review. Pain Med. 2007;8(Suppl 2):S50–62. https://doi.org/10.1111/j.1526-4637.2006.00179.x. PMID: 17714116
48. Romanovsky D, Cruz NF, Dienel GA, Dobretsov M. Mechanical hyperalgesia correlates with insulin deficiency in normoglycemic streptozotocin-treated rats. Neurobiol Dis. 2006;24(2):384–94. https://doi.org/10.1016/j.nbd.2006.07.009. Epub 2006 Aug 28. PMID: 16935517
49. Orestes P, Osuru HP, McIntire WE, Jacus MO, Salajegheh R, Jagodic MM, Choe W, Lee J, Lee SS, Rose KE, Poiro N, Digruccio MR, Krishnan K, Covey DF, Lee JH, Barrett PQ, Jevtovic-Todorovic V, Todorovic SM. Reversal of neuropathic pain in diabetes by targeting glycosylation of cav3.2 T-type calcium channels. Diabetes. 2013;62:3828–38.
50. Jensen TS, Karlsson P, Gylfadottir SS, Andersen ST, Bennett DL, Tankisi H, Finnerup NB, Terkelsen AJ, Khan K, Themistocleous AC, Kristensen AG, Itani M, Sindrup SH, Andersen H, Charles M, Feldman EL, Callaghan BC. Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management. Brain. 2021;12:awab079. https://doi.org/10.1093/brain/awab079. Epub ahead of print. PMID: 33711103
51. Yang Y, Dib-Hajj SD, Zhang J, Zhang Y, Tyrrell L, Estacion M, Waxman SG. Structural modelling and mutant cycle analysis predict pharmacoresponsiveness of a Na(V)1.7 mutant channel. Nat Commun. 2012;3:1186. https://doi.org/10.1038/ncomms2184. PMID: 23149731; PMCID: PMC3530897
52. de Greef BTA, Hoeijmakers JGJ, Geerts M, Oakes M, Church TJE, Waxman SG, Dib-Hajj SD, Faber CG, Merkies ISJ. Lacosamide in patients with Nav1.7 mutations-related small fibre neuropathy: a randomized controlled trial. Brain. 2019;142(2):263–75. https://doi.org/10.1093/brain/awy329. PMID: 30649227
53. Yuan RY, Sheu JJ, Yu JM, Chen WT, Tseng IJ, Chang HH, Hu CJ. Botulinum toxin for for diabetic neuropathic pain: a randomized double-blind crossover trial. Neurology. 2009;72:1473–8.
54. Chen WT, Yuan RY, Chiang SC, Sheu JJ, Yu JM, Tseng IJ, Yang SK, Chang HH, Hu CJ. OnabotulinumtoxinA improves tactile and mechanical pain perception in painful diabetic polyneuropathy. Clin J Pain. 2013;29:305–10.

55. Ghasemi M, Ansari M, Basiri K, Shaigannejad V. The effects of intradermal botulinum toxin type a injections on pain symptoms of patients with diabetic neuropathy. J Res Med Sci. 2014;19(2):106–11. PMID: 24778662; PMCID: PMC3999594
56. Restivo DA, Casabona A, Frittitta L, Belfiore A, Le Moli R, Gullo D, Vigneri R. Efficacy of botulinum toxin a for treating cramps in diabetic neuropathy. Ann Neurol. 2018;84(5):674–82. https://doi.org/10.1002/ana.25340. Epub 2018 Oct 16. PMID: 30225985
57. Salehi H, Moussaei M, Kamiab Z, Vakilian A. The effects of botulinum toxin type A injection on pain symptoms, quality of life, and sleep quality of patients with diabetic neuropathy: a randomized double-blind clinical trial. Iran J Neurol. 2019;18(3):99–107. PMID: 31749930; PMCID: PMC6858596
58. Taheri M, Sedaghat M, Solhpour A, Rostami P, Safarpour LB. The effect of intradermal botulinum toxin A injections on painful diabetic polyneuropathy. Diabetes Metab Syndr. 2020;14(6):1823–8. https://doi.org/10.1016/j.dsx.2020.09.019. Epub 2020 Sep 14. PMID: 32961514
59. Harden NR, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. 2010;150(2):268–74. https://doi.org/10.1016/j.pain.2010.04.030. Epub 2010 May 20. PMID: 20493633; PMCID: PMC2914601
60. Cutts S, Gangoo S, Srinivasan SH, Modi N, Pasapula C, Power D. Complex regional pain syndrome: an evolving perspective. Postgrad Med J. 2021;97(1146):250–5. https://doi.org/10.1136/postgradmedj-2020-137808. Epub 2020 Nov 12. PMID: 33184132
61. Harden RN, Oaklander AL, Burton AW, Perez RS, Richardson K, Swan M, Barthel J, Costa B, Graciosa JR, Bruehl S. Reflex Sympathetic Dystrophy Syndrome Association. Complex regional pain syndrome: practical diagnostic and treatment guidelines. Pain Med. 2013;14:180–229.
62. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet. 1993;342(8878):1012–6. https://doi.org/10.1016/0140-6736(93)92877-v. PMID: 8105263
63. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain. 2003;103(1–2):199–207. https://doi.org/10.1016/s0304-3959(03)00065-4. PMID: 12749974
64. de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. Pain. 2007;129(1–2):12–20. https://doi.org/10.1016/j.pain.2006.09.008. Epub 2006 Nov 7. PMID: 17084977
65. Schwartzman RJ, Erwin KL, Alexander GM. The natural history of complex regional pain syndrome. Clin J Pain. 2009;25(4):273–80. https://doi.org/10.1097/AJP.0b013e31818ecea5. PMID: 19590474
66. Weber M, Birklein F, Neundörfer B, Schmelz M. Facilitated neurogenic inflammation in complex regional pain syndrome. Pain. 2001;91:251–7.
67. Coderre TJ, Xanthos DN, Francis L, Bennett GJ. Chronic post-ischemia pain (CPIP): a novel animal model of complex regional pain syndrome-type I (CRPS-I; reflex sympathetic dystrophy) produced by prolonged hindpaw ischemia and reperfusion in the rat. Pain. 2004;112:94–105.
68. Del Valle L, Schwartzman RJ, Alexander G. Spinal cord histopathological alterations in a patient with longstanding complex regional pain syndrome. Brain Behav Immun. 2009;23:85–91.
69. Farzad M, Layeghi F, Hosseini A, Dianat A, Ahrari N, Rassafiani M, Mirzaei H. Investigate the effect of psychological factors in development of complex regional pain syndrome type I in patients with fracture of the distal radius: a prospective study. J Hand Surg Asian Pac. 2018;23(4):554–61. https://doi.org/10.1142/S2424835518500571. PMID: 30428789

70. Smart KM, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. Cochrane Database Syst Rev. 2016;2:CD010853. https://doi.org/10.1002/14651858.CD010853.pub2. PMID: 26905470
71. Forouzanfar T, van Kleef M, Weber WE. Radiofrequency lesions of the stellate ganglion in chronic pain syndromes: retrospective analysis of clinical efficacy in 86 patients. Clin J Pain. 2000;16(2):164–8. https://doi.org/10.1097/00002508-200006000-00010. PMID: 10870729
72. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. 2009;147:107–15.
73. Goebel A, Baranowski A, Maurer K, Ghiai A, McCabe C, Ambler G. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Ann Intern Med. 2010;152:152–8.
74. Aradillas E, Schwartzman RJ, Grothusen JR, Goebel A, Alexander GM. Plasma exchange therapy in patients with complex regional pain syndrome. Pain Physician. 2015;18(4):383–94. PMID: 26218942
75. Argoff CE. A focused review on the use of botulinum toxins for neuropathic pain. Clin J Pain. 2002;18(6 Suppl):S177–81.
76. Birthi P, Sloan P, Salles S. Subcutaneous botulinum toxin A for the treatment of refractory complex regional pain syndrome. PM R. 2012;4(6):446–9. https://doi.org/10.1016/j.pmrj.2011.12.010. PMID: 22732156
77. Lessard L, Bartow MJ, Lee J, Diaz-Abel J, Tessler OES. Botulinum toxin A: a novel therapeutic modality for upper extremity chronic regional pain syndrome. Plast Reconstr Surg Glob Open. 2018;6(10):e1847. https://doi.org/10.1097/GOX.0000000000001847. PMID: 30534480; PMCID: PMC6250468
78. Bellon G, Venturin A, Masiero S, Del Felice A. Intra-articular botulinum toxin injection in complex regional pain syndrome: case report and review of the literature. Toxicon. 2019;159:41–4. https://doi.org/10.1016/j.toxicon.2019.01.002. Epub 2019 Jan 17. PMID: 30660558
79. Kharkar S, Ambady P, Venkatesh Y, Schwartzman RJ. Intramuscular botulinum toxin in complex regional pain syndrome: case series and literature review. Pain Physician. 2011;14(5):419–24. PMID: 21927045
80. Safarpour D, Jabbari B. Botulinum toxin A (Botox) for treatment of proximal myofascial pain in complex regional pain syndrome: two cases. Pain Med. 2010;11:1415–8.
81. Carroll I, Clark JD, Mackey S. Sympathetic block with botulinum toxin to treat complex regional pain syndrome. Ann Neurol. 2009;65(3):348–51. https://doi.org/10.1002/ana.21601. PMID: 19334078; PMCID: PMC2763598
82. Lee Y, Lee CJ, Choi E, Lee PB, Lee HJ, Nahm FS. Lumbar sympathetic block with botulinum toxin type A and type B for the complex regional pain syndrome. Toxins (Basel). 2018;10(4):164. https://doi.org/10.3390/toxins10040164. PMID: 29671801; PMCID: PMC5923330
83. Bellon G, Venturin A, Masiero S, Del Felice A. Intra-articular botulinum toxin injection in complex regional pain syndrome: case report and review of the literature. Toxicon. 2019;159:41–4. https://doi.org/10.1016/j.toxicon.2019.01.002. Epub 2019 Jan 17. PMID: 30660558
84. Yoo Y, Lee CS, Kim J, Jo D, Moon JY. Botulinum toxin type a for lumbar sympathetic ganglion block in complex regional pain syndrome: a randomized trial. Anesthesiology. 2021; https://doi.org/10.1097/ALN.0000000000004084. Epub ahead of print. PMID: 34890455
85. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil. 2008;89:422–9.
86. Carlen PL, Wall PD, Nadvorna H, Steinbach T. Phantom limbs and related phenomena in recent traumatic amputations. Neurology. 1978;28:211–7.
87. Jensen TS, Krebs B, Nielsen J, Rasmussen P. Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation. Pain. 1983;17:243–56.

88. Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. J Pain Res. 2013;6:121–36.
89. Sperry BP, Cheney CW, Kuo KT, Clements N, Burnham T, Conger A, Cushman DM, McCormick ZL. Percutaneous treatments for residual and/or phantom limb pain in adults with lower-extremity amputations: a narrative review. PM R. 2021; https://doi.org/10.1002/pmrj.12722. Epub ahead of print. PMID: 34628724
90. Elavarasi A, Goyal V. Botulinum toxin to treat phantom limb pain. Toxicon. 2021;195:17–9. https://doi.org/10.1016/j.toxicon.2021.02.010. Epub 2021 Feb 19. . PMID: 33610636
91. Alviar MJ, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. Cochrane Database Syst Rev. 2016;10(10):CD006380. https://doi.org/10.1002/14651858.CD006380.pub3. PMID: 27737513; PMCID: PMC6472447
92. Kern U, Martin C, Scheicher S, Müller H. Effects of botulinum toxin type B on stump pain and involuntary movements of the stump. J Phys Med Rehabil. 2004;83:396–9.
93. Jin L, Kollewe K, Krampfl K, Dengler R, Mohammadi B. Treatment of phantom limb pain with botulinum toxin type A. Pain Med. 2009;10:300–3.
94. Wu H, Sultana R, Taylor KB, Szabo A. A prospective randomized double-blinded pilot study to examine the effect of botulinum toxin type A injection versus Lidocaine/Depomedrol injection on residual and phantom limb pain: initial report. Clin J Pain. 2012;28:108–12.

Chapter 5
Botulinum Toxin Treatment in Migraine and Other Headaches

Headache is a common human ailment with an annual prevalence of 90% and life time prevalence of 99% [1]. The latest international classification of headaches (third edition, 2018), published by the International Headache Society (IHS), defines 10 primary and 14 categories of secondary headaches [2]. The focus of this chapter is on botulinum toxin treatment of primary headaches, especially migraine and tension headache, where extensive data regarding botulinum toxin therapy are available. A method of injection for chronic migraine designed by the author with fewer numbers of injections (compared to PREEMPT) and comparable efficacy is described. The limited literature on botulinum toxin treatment of cluster headaches and posttraumatic headaches is also discussed.

Migraine

Introduction

Migraine is a common primary headache disorder that affects 18% of women and 6% of men [3]. It is the most complex form of human headache due to the great variability of its symptoms. Migraine has a global prevalence of 1 billion and is the major cause of medical disability during the reproductive years (ages 20–55) years [4]. It is a major financial burden to society with an estimated annual cost of $4.2 billion for direct cost of care in the United States [5].

Migraine headache is subclassified into migraine with aura (MWA) and migraine without aura (MWoA). The pain is characteristically pulsating, starts often unilaterally, and is frequently associated with photophobia, phonophobia, and gastrointestinal distress. Migraine's aura often involves the visual system with either enhancement of function (bright or zigzag lights) or loss of function (scotoma). Loss of function may also occur in the motor (hemiplegic migraine) or somatosensory domains.

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_5

Local scalp tenderness and allodynia (touch perceived as pain) are common in migraine and have been reported to affect 43% of 89 patients in one study [6]. In another study, the incidence of scalp tenderness increased with the number of migraine attacks: 33% associated with 1 to 4 attacks and 58% associated with more than 8 attacks/month [7]. Allodynia usually starts ipsilateral to the side of headache, denoting activation of peripheral nociceptive pathways. Contralateral spread of allodynia indicates central sensitization to pain via third-order (thalamic) neurons [8].

In episodic migraine, migraine attacks occur less than 15 days per month. Chronic migraine (CM) is defined as a headache disorder with headaches occurring 15 or more days per month for a minimum of 3 months with 8 or more headache days/month that meet the criteria of migraine [9]. Chronic migraine includes approximately half of all chronic daily headaches and has an estimated global prevalence of 2% [10]. It is the most costly form of migraine with nearly $200 per week more cost to the employers than episodic migraine [11].

Pathophysiology The aura phase of migraine corresponds to the electrical phenomenon of cortical spreading depression (SD) that often involves the occipital cortex leading to visual symptoms [12]. Spreading depression marches through the cortex at the rate of 3 to 6 mm per minute and does not respect specific vascular territories [13]. What triggers and initiates SD is still open to discussion and speculation. It is believed that the extracellular release of potassium, nitric oxide, adenosine, and others agents during cortical depression causes inflammation and vasodilation in the cortex and meningeal vessels [14]. This results in a sensitized trigeminovascular system which sends enhanced afferent impulses to the trigeminal ganglion, nucleus pontis caudalis, superior salivatory nucleus, and parasympathetic efferent fibers [15]. Excitation of the latter causes dural vasodilation. Emergence of nociceptive stimuli at different levels of the nervous system and the trigeminal nucleus causes head and facial pain.

In a review of genetic migraine, Silberstein and Dodick [16] noted that first-degree relatives of patients with MWA and MWoA have 4 and 1.9 times the risk of developing the same type of migraine as their affected family members, respectively. Approximately 52% of female twins raised together or apart demonstrate co-occurrence of similar headaches. Aside from familial hemiplegic migraine which is monogenic (with three identified genes), the genetics of other forms of migraine is complex and the information is still preliminary and evolving. A mutation of CNK18 gene with complete loss of function of related K channel has been detected in some patients with MWA [17].

Reliable biomarkers for diagnosis of migraine are often sought. In one study, serum level of calcitonin gene-related peptide (CGRP) was 2.5 times higher in CM patients compared to asymptomatic controls and about 1.8 times higher than patients with episodic migraine or cluster headaches ($P < 0.05$) [18]. CGRP level elevation during ictal and interictal periods, however, is debatable, and the published reports have described contradictory results. Recently, Latif et al. [19] reported an increase in serum level of ApoE in both ictal and interictal phase of migraine, but CGRP increase was noted only during the ictal phase.

Treatment

Treatment of migraine headaches includes strategies to abort acute attacks and, in case of frequent attacks, to reduce the frequency of attacks by daily medications [20, 21]. Treatment of mild migraine attacks includes use of acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs). For more severe attacks not responding to these measures, triptans are often recommended. Triptans act on 5HT receptors in the trigeminal nucleus caudalis and in the dorsal horns of the upper cervical spine, hence interfering with the nociceptive cascade beginning to set in the trigeminovascular system [22]. Many patients with migraine, however, do not respond to triptans, and cardiovascular comorbidities often limit their use [23]. For attacks refractory to oral medications, liberal hydration (IV fluids) and intravenous administration of dopamine receptor agonists (prochlorperazine), dihydroergotamine (DHE), or IV nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac or ketorolac are recommended [24]. One small study has shown that high flow oxygen may alleviate acute attacks of migraine [25]. Opioids, barbiturates, and a short course of steroids are also used as abortive therapy by some clinicians, but supportive studies are lacking.

Preventive daily treatment of migraine is recommended when migraine episodes exceed six to eight headache days per month or if the patient has to use abortive medications more than eight to nine times per month [26]. Beta blockers such as propranolol or metoprolol, topiramate, gabapentin, amitriptyline, and sodium valproate are commonly used for migraine prevention [27]. Venlafaxine and histamine are considered second-line preventive medicine.

For chronic migraine, two multicenter, double-blind studies in large cohorts have shown the efficacy of topiramate in reducing the number of pain days per month (3 days per month versus 0.7 days per month for placebo in the US study) [21, 28]. The effective dose was 100 mg/day.

Two other blinded studies performed in small cohorts of 41 and 71 patients strongly suggested efficacy of valproate and levetiracetam in chronic migraine, respectively [29, 30]. The study using valproate [29] had a parallel design, while the study of levetiracetam [30] had a cross-over design. In the valproate study, treatment significantly reduced both headache days per month and the headache intensity. In the case of levetiracetam, the primary endpoint—absence of any headaches—was not met, however, perhaps due to the rigidity of criteria.

Therapeutic Use of Calcitonin Gene-Related Peptide (CGRP) Inhibitors

CGRP is a pain neurotransmitter found in abundance in the peripheral and central nervous systems as well as sensory nerves that supply the meninges. It is believed that CGRP plays an important role in the pathophysiology of migraine. As

Table 5.1 CGRP-blocking agents and their date of FDA approval for treatment of migraine

Generic name	Trade name	Date of approval by FDA
Erenumab-aooe	Aimovig	4-17-2018
Fremanezumab	Ajovy	9-14-2018
Galcanezumab-glnm	Emgality	9-17-2018
Ubrogepant	Ubrely	12-23-2019
Epitinezumab-jjmr	Vyepti	2-21-2020
Rimegepant sulfate	NurtecODT	2-27-2020

mentioned before, high CGRP levels are found in patients with chronic migraine and during acute migraine attack (ictal period). Since approval of CGRP inhibitor erenumab by the FDA in 2018, several other CGRP-blocking drugs have received subsequent approval (Table 5.1) making CGRP inhibitors major therapeutic agents for preventive and abortive treatment of migraine. CGRP inhibitors have large or small molecules. The ones with large molecules are monoclonal antibodies and those with small molecules are called gepants. The large monoclonal antibodies target either CGRP or CGRP receptor and are used mainly as a preventive drug for migraine treatment. They work on the sensory nerve supply of the meninges and, in order to avoid degradation in the stomach, are injected subcutaneously. These CGRP-blocking agents take longer to work because of their large molecule but cause less liver and kidney damage.

Gepants are CGRP inhibitors with small molecules. After blocking CGRP receptor, they are able to relieve acute migraine attacks as well as preventing recurrence of migraine. Gepants quickly enter the brain and thus work fast after administration. Gepants are metabolized in the liver, and, therefore, have a potential for damaging the liver, although with newer gepants, this risk has been substantially reduced. For this reason, new gepants are becoming major drugs for treatment of acute migraine attacks. Recently, Zizhen et al. [31], in a meta-analysis paper, reviewed the efficacy and side effects of Ubrogepant in treatment of migraine. The data were analyzed from five randomized clinical trials including 4903 patients. At 2 h post dose, the percentage of patients having pain relief, absent photophobia, nausea, and phonophobia was significantly higher in patients receiving Ubrogepant compared to placebo ($P < 0.0001$); the incidence of common side effects was similar between the two groups ($P > 0.5$).

Erenumab, the first FDA-approved CGRP inhibitor, unlike the other three CGRP inhibitors, blocks CGRP receptor rather deactivating the ligand itself. The drug is provided in 70 and 140 mg doses prescribed as monthly injections. The starting dose is 70 mg. In a large phase III study that led to its FDA approval, erenumab decreased the number of pain days significantly in episodic migraine by 3.2 vs. 1.8 and 3.7 vs. 1.8 compared to placebo for 70 and 140 mg doses, respectively. Among patients in 70 mg group, 43.3% had 50% or greater reduction of mean number of migraine days, while 50% of the 140 mg group experienced the same reduction ($P < 0.0001$) [32]. In a large real-life experience study including a cohort of 29,451, those patients who took erenumab for migraine treatment demonstrated better

adherence to erenumab compared to all other drugs previously used for treatment of migraine, though the adherence was still considered low [33]. Among patients treated with erenumab, 48.7% were able to withdraw from medications used for acute migraine attacks; approximately one-third of the patients were able to come off triptans or opioids. Side effects of erenumab noted in 1% or more of treated patients include injection site reaction (5–6%), constipation, nausea, and dizziness. Long-term follow-ups of 5 years and more are not yet available for treatment with erenumab.

Botulinum Neurotoxin for Preventive Treatment of Migraine

Episodic Migraine (EM)

The first double-blind, placebo-controlled, prospective study investigating the efficacy of onabotulinumtoxinA (onaA) in episodic migraine was published in 2000 [34]. The authors investigated the effect of 25 and 75 units of onaA in 123 patients with 2 to 8 migraine attacks per month. Patients with headache days exceeding 15/month (chronic migraine) were excluded. OnaA was injected into the procerus muscle (3–9 units total) and bilaterally into corrugators (two on each side—6 or 18 units total), frontalis (two on each side, 6 unit or 18 units total), and temporalis (one on each side, 6 or 18 units total) muscles.

Primary efficacy was defined as a significant change from the baseline of migraine attacks. At 3 months, patients in the 25-unit group had significant reduction in headache frequency and headache intensity, and 50% reduction of headache frequency compared to baseline. No statistically significant change was noted in the 75-unit group, a finding attributed to their milder headaches at baseline. Subsequently, two large class I studies were conducted with onaA in EM investigating 238 and 418 patients, respectively [35, 36]. Both studies failed to meet their primary outcome measure, which was reduction of migraine frequency/month. Another small (60 patients) class II study of EM that considered 50% or more reduction of migraine frequency as the primary outcome also failed to meet its primary endpoint [37]. The total dose applied in the aforementioned studies varied from 25 to 100 units. The American Academy of Neurology's subcommittee on guidelines, based on the above four studies (two class I and two class II), assigned Level B evidence (probably ineffective) to onaA for treatment of episodic migraine [38].

Two other class I studies which were published later and used larger doses of onaA confirmed the stance of AAN's subcommittee on episodic migraine [39, 40]. The first study compared the effect of different doses of onaA (75, 150, and 225 units) with placebo using the mean number of migraine days at day 180 as the primary outcome measure. All four groups (including three toxin and one placebo) improved with either onaA or saline (the placebo), and there was no significant difference between onaA subgroups and the placebo group [39]. In the second study of

369 patients [40], the authors compared the effect of onaA (mean 190.5 units) with placebo. The primary endpoint, defined as the mean change in migraine episodes over 30 days, was not met. Although the study failed to meet the primary endpoint, a subgroup analysis of patients with 12 to 14 headache days per month showed significant improvement in onaA group versus the placebo ($P = 0.04$).

Blumenfeld et al. [41] studied 59 patients with episodic migraine under a double-blind, parallel design protocol. The effect of onabotulinumtoxinA (onaA) was compared with that of divalproex sodium; 30 patients received onaA, and 29 patients received divalproex sodium. The study group consisted of 84.7% females. OnaA was injected into procerus, corrugators, frontalis, temporalis, splenius capitis, sternocleidomastoid, trapezius, occipitalis, cervical paraspinals, semispinalis capitis, and masseter muscles. The dose of divalproex was 250 mg was twice daily, and the dose of onaA was variable depending on the size of the muscle; for instance, it was 25 units for frontalis (both sides) and 7.5 to 20 units for temporalis muscles. The total dose of onaA was 100 units. Outcome measures consisted of reduction of headache days per month, maximum headache severity, and overall headache index. A number of other outcome measures including quality of life were also assessed as secondary outcomes. The patients' response rate to both treatments was comparable; it was 18.2% for onaA and 23.8% for divalproex. A significantly larger number of patients who were injected with divalproex discontinued the treatment compared to those who were treated with onaA (27.6% vs. 3.3%, respectively).

Comment

Placebo-controlled studies of botulinum toxin-A in episodic migraine disclosed disappointing results. However, a controlled study with design of PREEMPT studies that had shown efficacy in chronic migraine has not been performed in episodic migraine. Nevertheless, in one study [41], patients with episodic migraine experiencing 12 to 14 pain days per month responded significantly to onaA treatment.

Chronic Migraine

In 2004, we had shown that pericranial injection of onabotulinumtoxinA can improve migraine index (a measure of both migraine intensity and frequency) in a small blinded study [42]. The study group consisted of 32 patients with migraine attacks of >5/month; some of them had chronic migraine. No significant change on the number of headache days or migraine days per se was noted. In 2008, Freitag et al. [43] compared the effect of fixed dose (100 units) and fixed site (glabella, frontalis, temporalis, trapezius, and suboccipital) injections between onaA (20 patients) and placebo (21 patients) with chronic migraine. Patients with medication overuse were excluded. The primary outcome was the number of migraine episodes

within each 4 weeks of the study. The secondary outcomes included the number of headache days and the headache index (a measure of both intensity and frequency). OnaA was statistically superior to placebo on both primary outcome ($P < 0.01$) and secondary outcomes ($P = 0.041$ and $P = 0.046$). Nevertheless, between 2002 and 2009, a number of large multicenter studies assessing efficacy of BoNTs in chronic migraine failed to meet their primary outcome.

The major breakthrough in this area came with the publication of PREEMPT studies (I and II) in summer of 2010 [44, 45]. Each of these two multicenter studies evaluated over 600 patients (total 1384 patients) who met the criteria for chronic migraine. Patients with medication overuse were included in both studies. The studies had a 24-week blinded arm followed by 32 weeks of open arm. The primary outcome for PREEMPT I was the number of migraine episodes and for PREEMPT II, the number of headache days, both evaluated at 24 weeks. A number of secondary outcomes were also evaluated at 24-week postinjection. PREEMPT II met both its primary and secondary outcomes at all time points. For the primary outcome, the reduction in headache days was 9 for onabotulinumtoxinA versus 6.7 for the placebo ($P < 0.001$). Although PREEMPT I did not meet its primary outcome, it met all its secondary outcomes. The pooled data [46] from the two studies showed significant change from the baseline in favor of onabotulinumtoxinA in respect to the primary and all secondary parameters (Fig. 5.1). Based on these studies, onabotulinumtoxinA was approved for treatment of chronic migraine in the UK, Canada (summer of 2010), and in the United States (October 2010).

Over the next 10 years, through tireless efforts of PREEMPT investigators, the effects of onabotulinumtoxin injections on many aspects of migraine were investigated and published using the PREEMPT cohort or its subgroups. Lipton et al. [47] studied the PREEMPT pooled data (1384 patients) specifically in regard to the quality of life which was measured by both the Migraine Specific Quality of Life Questionnaire (MSQ) and the Headache Impact Test (HIT). Both measures were significantly improved from the baseline in the onaA-treated group at 24 weeks providing strong evidence for quality of life improvement with onaA injections in chronic migraine. In a recent assessment of the 1384 patients who had participated

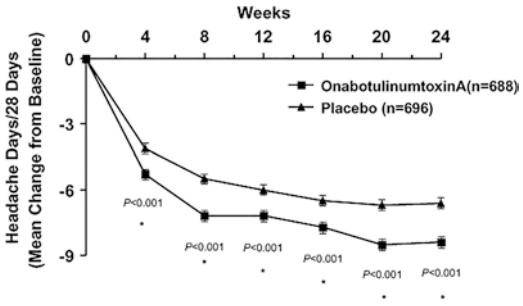

Fig. 5.1 Pooled data from two PREEMPT studies show statistically significant reduction of headache days in onabotulinumtoxinA (Botox) group at all time points from week 4 to week 24 post injection [46]. (Reprinted with permission from publisher (Wiley-Blackwell))

in the PREEMPT trial, the authors found that nonresponders—defined as failing to have reduction in headaches days/month compared to placebo—were found to show significant improvement in other aspects of migraine such as improvement of quality of life, patient's emotional state, and headache impact scores [48]. The authors concluded that their findings implied that the full benefits of onabotulinumtoxinA are not captured by headache day reduction (which was the primary outcome measure of PREEMPT study) because many nonresponders demonstrated improvement in other important issues associated with migraine. In another study from the same group [49], reassessment of PREEMPT cohort showed that significant reduction of pain days and migraine days started as early as 7 days after injection of onabotulinumtoxinA with progressive improvements over subsequent injections. The findings emphasized early onset of onaA effect and more reduction in headache days with subsequent injections.

BoNT Injection Technique in Chronic Migraine

A variety of injection techniques have been proposed for treatment of chronic migraine based on established studies and the practice of experienced toxin injectors. The technique used in PREEMPT studies [50] recommends 31 injection sites, and injection of five units per site for a total dose of 155 units (Table 5.2). In some patients (depending on weight and other factors), an additional 40 units are allowed for a total of 195 units. A dilution of 100 units/2 cc was recommended. Shortly after publication of PREEMPT results, PREEMPT technique was adopted and endorsed by migraine specialists [51].

Table 5.2 Injection paradigm recommended by the PREEMPT study: injected muscles, muscle location, muscle function, and the dose of onabotulinumtoxinA (Botox) administered per site(s)

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

The large number of injections in PREEMPT protocol (31 sites) is often an issue with migraine sufferers; therefore, in current practice, some clinicians prefer to use fewer number of injections. I have introduced a technique that provides similar results to PREEMPT studies with fewer numbers of injections. This technique was initiated by us at Walter Reed Army Medical Center, Washington, D.C. (2000–2004), and then practiced at Yale University during my tenure as director of botulinum toxin treatment program (2004–2015). Modified slightly over years, the last version of this technique endorses 19 injection sites (Fig. 5.2). The total dose is 175 units. In this injection paradigm, 5 units are injected into each corrugator muscle, 5 units

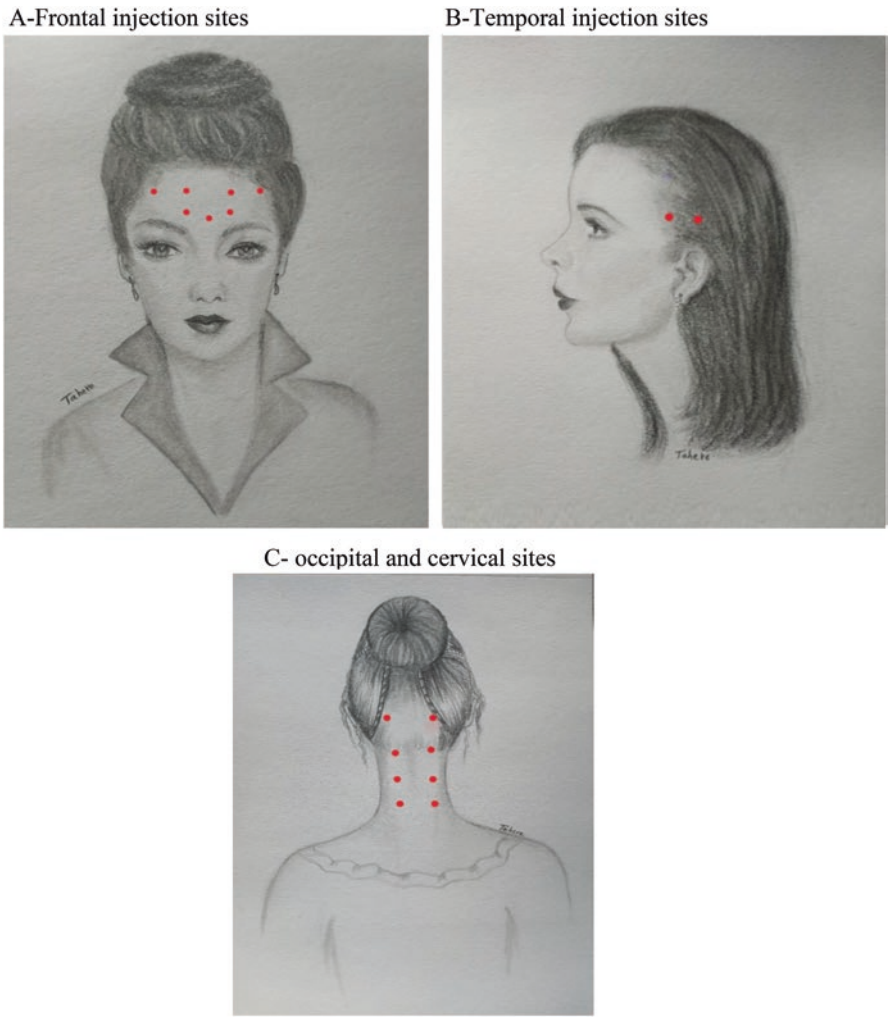

Fig. 5.2 Injection sites recommended by Walter Reed-Yale technique. (**a**) Frontal injection sites. (**b**) Temporal injection sites. (**c**) Occipital and cervical sites

into the procerus muscle at midline, 20 units into the frontalis muscle (5 units/site, 4 sites similar to PREEMPT), 30 units into temporalis muscles (15 units anterior and 15 units midtemporal (two injections/side), 10 units into each occipitalis (one injection/site), and 30 units/side into the splenius muscles of the neck (10 units per each of three sites) (Fig. 5.2). Trapezius muscle injections are excluded. The logic of this injection paradigm is as follows:

1. Occipitalis muscle is a small muscle and, in my opinion, one injection with a larger dose provides sufficient diffusion into the muscle and overlaying skin.
2. In the temporal area, the low midtemporal site (one of four injections sites in PREEMPT), probably does not contribute much to pain relief as it may very well be the area of temporalis tendon rather than the temporalis muscle. It has been shown in cadaver studies that in many individuals, the temporalis tendon is large and occupies this area (Fig. 5.3) [52].
3. Trapezius muscles (areas) are omitted from this injection paradigm since their contribution to chronic migraine is debatable. Instead, cervical injection sites are increased from two to three and include mid- and lower cervical regions (Fig. 5.2) with an increase in cervical site doses from 5 units/site (PREEMPT) to 10 units/site.

In an open-label study of 50 patients with chronic migraine when using this Walter Reed-Yale technique, 72% of the patients after the first injection and 85% after the third injection reported their experience after onaA treatment as " very satisfactory" using Patient Global Impression of Change (PGIC) [53]. No serious side effects were reported over 2 to 8 years of follow-up observation. After the first year of treatment, 73% of the patients reported no more emergency department visits for additional therapy. By 12 months of treatment, 50% of the patients discontinued their daily preventive medications and 61% no longer had any need for

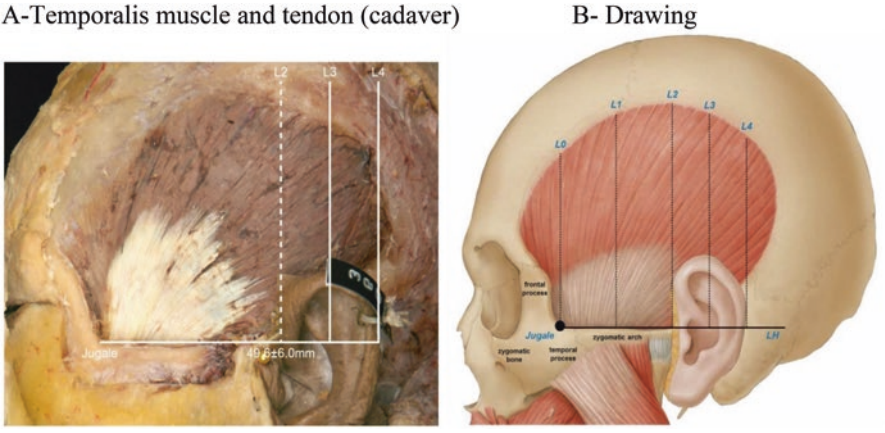

Fig. 5.3 From Choi et al. 2016 [52]. Reproduced under creative commons attribution. Courtesy of "Toxins" and publisher. (**a**) Temporalis muscle and tendon (cadaver). (**b**) Drawing

abortive medicine. In a subsequent double-blind, placebo-controlled study of 25 patients [54], injections of onaA, using the Walter Reed-Yale technique, reduced the headache days significantly compared to the placebo at 4 and 8 weeks post injection ($P = 0.0031$). Using PGIC, 9 of 11 patients in the onaA group and 3 of 10 patients in the placebo group described their experience as very satisfactory ($P = 0.030$). In the open arm of the study, 58.8% of the patients reported 50% or more reduction of pain days at 4 weeks post injection and 88.2% demonstrated reduction of HIT scores compared to baseline.

I have used the above-mentioned Walter Reed-Yale technique in hundreds of patients including thousands of injections sessions over a period of nearly 20 years. The results have been similar to PREEMPT technique (see above). I have not seen any serious side effects.

Some authors [55] have warned against development of weakness in cervical and trapezius muscles if the dose per injection site exceeds 5 units. I have never observed weakness of these muscles following injection of 10 units/site, either in migraine and or in any other disease conditions (i.e., dystonias). This is probably because cervical paraspinal muscles are very strong, multilayered, closely attached and supported by deeper paraspinal muscles. Nevertheless, in rare instances among patients with exceptionally thin necks, it may be prudent to reduce the neck injection dose/site to 5 units. In such cases, the total dose per session would be 1450 units (for onabotulinumtoxinA) rather than 175 units.

Patient Report

A 32-year-old female complained of frequent migraine attacks over the past 7 years. The attacks gradually increased in frequency despite taking triptans for acute attacks as well as a number of preventive medications. The last preventive drug she had used prior to initiation of BoNT treatment was topiramate, 100 mg daily. The patient experienced daily headaches with three to four severe migraine episodes per week. During the episodes, she had pounding/pulsating headaches with nausea and photophobia. She had to stop working 2 years ago due to disabling headaches. After the second session of botulinum toxin treatment with onaA (a total dose of 180 units) using the Walter-Reed/Yale technique, she reported significant reduction in frequency and intensity of the headaches that improved even further with subsequent treatments. A year after initiation of treatment with onaA, she was able to stop all preventive medications. Six months later, she resumed her work and became gainfully employed. She continued to have onaA injections for migraine every 3–4 months. When last seen, 4 years after initiation of BoNT therapy, she reported two to three minor headaches per month. She was fully functional and employed and expressed relief and gratitude.

In recent years, other techniques have been suggested as an alternative to the PREEMPT technique. Zhang et al. [56] have shown that most pericranial pain fibers

are located along the skull's suture lines and injecting along the suture lines is more effective in reducing the sensitivity of meningeal chemical nociceptives in rats. Kara et al. [57] suggested injecting six sites along the suture lines under ultrasound guidance for treatment of chronic migraine. Kim et al. [58], based on the study of 25 human cadavers, suggested four temporal sites of injection for BoNT-A in chronic migraine slightly different from the temporal sites endorsed by the PREEMPT study.

The Issue of Medication Overuse in Chronic Migraine

Medication overuse is a common problem among many patients with chronic migraine. Some investigators questioned the inclusion of the patients with medication overuse headaches in PREEMPT studies. Silberstein et al. [59] studied the efficacy of onaA in a subgroup of PREEMPT study patients who had medication overuse in addition to chronic migraine (MO + CM). Of 1384 patients in the PREEMPT study, 65.3% met the criteria for medication overuse. At 24 weeks, similar to the patients in the main PREEMPT study, MO + CM patients demonstrated significant reduction of headache days (primary end point) (8.2 vs. 6.2 with $P < 0.001$) and also met many secondary endpoints (frequency of migraine days, frequency of moderate to severe headache days, cumulative headache hours on headache days, headache episodes, migraine episodes, and percentage of patients with severe headache impact test-6 (all Ps < 0.05). Triptan intake was also significantly reduced in the onaA-treated group ($P < 0.001$). The authors concluded that onaA treatment is effective in patients with chronic migraine and MO.

Sardini et al. [60] studied the effect of onaA injections in 68 patients with chronic migraine without aura and MO (35 placebo, 33 toxin). The study was double-blind and placebo-controlled with primary and secondary outcomes measured at 12 weeks post injection. Patients received a total of 16 injections (100 units), 8 on each side (2 frontal, 2 cervical, 1 corrugator, 1 temporal, 2 trapezius). No significant difference was noted between the placebo and toxin groups regarding reduction of pain days (primary outcome). A subgroup analysis of the data, however, demonstrated that MO patients with pericranial tenderness had significantly lower number of pain days (primary outcome) after onaA injections. The total dose of 100 units used in this study was probably too small; also, some important head regions (i.e. occipital) were not injected. In contrast to Silberstien et al. [59], in a recent double-blind study of 179 patients with chronic migraine and medication overuse, Pijpers et al. [61] have not found botulinum toxin-A in a dose of 155 units superior to placebo in reducing pain days per month (7 days vs. 6 days, $P > 0.5$). They suggested acute drug withdrawal first before subjecting the patients to expensive BoNT therapy. It should be noted, however, that in this study, a small dose of onaA (17.5) units was used as placebo.

Long-Term Response to BoNTs in Chronic Migraine and Safety Issues

Although many experienced practitioners using BoNTs in the treatment of migraine have long believed in the long-term efficacy and safety of onaA, until recently, no systematic data was available. In 2014, Aurora et al. [62] published data on safety, tolerability and efficacy of onaA (PREEMPT study) after 5 cycles of treatment (at 56 weeks). The mean change in frequency from baseline of headache days, migraine days, moderate to severe headache days and 50% or more change in headache days from baseline were all significantly lower ($P < 0.05$) in the onaA treatment group. The quality of life was further improved at 56 weeks (59%) compared to 25 weeks (44%), measured by 5 or more points increase in the HIT-6. No cumulative undesirable side effects were noted. Tolerability was excellent and there were no serious safety issues.

In my experience, minor side effects with botulinum injections for migraine are seen in approximately 10% of the patients; these include pain at the site of injection, minor bleeding, transient ptosis and transient elevation of the lateral part of the eyebrows. Ptosis can be avoided by avoiding low injections of corrugator muscles. Elevation of lateral part of both eyebrows (Mephisto sign- Fig. 5.4) can be corrected by injection of a small additional dose of the toxin into the lateral regions of the eyebrows [63].

Imploding Versus Exploding Migraine

In a study of 63 patients with migraine, Jakubowski et al. [64] found patients with imploding headaches to be better responders to onaA than those with exploding headaches. Among responders to onaA, 74% had imploding headaches, while

Fig. 5.4 Elevation of lateral part of the eyebrow after BoNT-A injection of frontalis muscle for treatment of chronic migraine. (**a**) Before BoNT injection. (**b**) After BoNT injection

among nonresponders, 92% had exploding headaches. Imploding headaches were described as those with pressure from outside the head (crushed, clamped or stabbed by an external force). Exploding headaches were headaches felt as pressure built inside of the head. This is an interesting and perhaps important concept. Distinction between exploding and imploding headaches is not always easy in patients with chronic migraine and requires focused questioning by the examining physicians.

BoNT Treatment in Pediatric Chronic Migraine

Emerging data suggest efficacy of BoNT therapy in pediatric migraine. The published data are, however, small and consist only of retrospective studies. The largest cohort has been reported recently in 2021 [65]. In this study, authors analyzed the effect of botulinum toxin-A (Botox) treatment in 65 children and adolescents, ages 11 to 18, who had been treated and observed between 2013 and 2018. The dose per kilogram was 2.8 units/kg mounting to an average total dose of 172 ± 35 units. Children's baseline average score in the visual analogue scale (VAS) representing pain severity was 7.7 ± 1.2. At 6 weeks after onaA injection, investigators noted an average decrease of 5.2 ± 2.2 in VAS. There was also a reduction in the number of pain days/month from 16 to 4. Two children demonstrated side effects. One complained of dizziness that cleared in 15 min; the other developed a low-grade fever associated with enlarged lymph nodes that resolved in 1 week. Two other smaller retrospective studies and two case reports also support the notion that treatment with onabotulinumtoxinA provides pain relief in children with chronic migraine [66].

Treatment of Chronic Migraine with Other Botulinum Toxins

IncobotulinumtoxinA (Xeomin)

In an open-label, prospective study, 50 patients with chronic headaches received incobotulinumtoxinA (Xeomin) injections into pericranial and cervical muscles using the technique of PREEMPT studies-31 injection sites [67]. The mean number of injections and duration of treatment per patient was 3.5 (range 2–13) and 21 (6–68) months, respectively. The total dose of incobotulinumtoxinA per session was 145 units. From baseline to first evaluation, 44 patients (73%) demonstrated >50% reduction in the frequency of migraine episodes, 29 patients (48%) showed >50% reduction in the number of headache days, and 28 patients (46%) experienced a > 50% reduction in drug intake for migraine. The authors concluded that due to

continued response over time "incobotulinumtoxinA seems to represent an effective and sustained prophylactic treatment for chronic migraine."

The Mechanism of Action of OnabotulinumtoxinA (onaA) in Chronic Migraine

In any chronic pain condition, both pain and pain maintenance result from the causative factors and mechanisms that induce that type of pain and to the degree of sensitization of the sensory and nociceptive system that develops over time. Peripheral and central sensitization play a major role in pain sustenance [68] (see Chap. 3). Animal investigations have demonstrated that peripheral injection of botulinum toxin-A interrupts the initial pathological event that leads to the development of migraine- that is meningioma-trigeminal inflammation [69]. Emerging data also indicate that peripheral injection of botulinum toxin-A can reduce both peripheral and central sensitization.

In animals, experimentally induced cortical spreading depression, an electrophysiological phenomenon observed at the onset of migraine headaches, releases pain transmitters (particularly CGRP) and proinflammatory agents in meningeal and dural nerve endings [70]. Blood CGRP levels are elevated in patients with chronic migraine, but not in episodic migraine [71]. Patients with higher CGRP levels respond better to botulinum toxin-A treatment [72].

The "inflammatory soup" that develops in the dura at the beginning of the migraine process irritates C- and A-delta nerve fibers that project to brainstem trigeminal nucleus resulting in headaches. In rats, it has been shown that after pericranial injection of botulinum toxins, cleaved SNAP25 colocalizes with CGRP in dural nerve endings and inhibits development of both dural inflammation and local increase of CGRP [73]. Matak et al. [74, 75], in a series of animal studies, have shown that after peripheral injection of botulinum toxin (rat's whisker and other models), cleaved SNAP25 can be found in trigeminal nucleus and such injections also change the neuronal activity of periaqueductal gray matter in the midbrain, another potential site for its analgesic effects. Trigeminal afferent fibers consist of small C and A-delta fibers and use a variety of neurotransmitters (among them are CGRP, glutamate and substance P) as their signaling messengers [76]. Several animal experiments have shown that peripheral injection of botulinum toxins (both A and B) can suppress the release of glutamate and substance P from peripheral nerve endings, dorsal sensory ganglia and at the spinal cord level [77–79].

Another mechanism through which botulinum neurotoxin injection can alleviate migraine is via action of the toxin upon specific pain receptors that are present on dural C fibers-these include two groups of pain receptors namely TRPA1 from cation channel vanilloid family and P2X3 from ATP-gated PTX receptor cation family (purinergic). It has been shown that peripheral injection of botulinum toxin-A can

block the insertion of these receptors to the cell membrane by vesicles [80]. Extracranial injection of botulinum toxin-A inhibits intracranial meningeal responses to TRPV1 and TRPA1 channels [56]. In a study of 63 patients with chronic migraine treated with botulinum toxin-A, Dominguez et al. [81] found that those patients who responded to treatment (78.3%) had a higher baseline serum level of P2X3 (>1000 picogram/ml, $P < 0.001$).

Drinovac et al. [82] investigated the effects of opioid system on the analgesic effect of botulinum toxin-A by recording c-Fos expression in the spinal cord- a measure that represents neuronal activation. Administration of nonselective opioid antagonist naltrexone prevented the antinociceptive effects of BoNT-A in formalin and sciatic nerve transection-induced pain. Also, this pain reduction, after BoNT-A injection, did not occur when either naltrexone or selective μ-antagonist naloxonazine was injected intrathecally. The authors concluded that the central antinociceptive action of botulinum toxin A might be associated with the activity of the endogenous opioid system.

Factors that reduce central sensitization also potentially contribute to pain relief in chronic migraine. Intramuscular injection of botulinum toxins has been shown to significantly reduce the activity of intrafusal muscle fibers [83] that constantly report the length of the muscle to the spinal neurons. Reduction of this powerful input to already sensitized spinal sensory neurons can substantially reduce central sensitization [84]. It has been suggested that relief of chronic migraine results from blocking the release of pain transmitters at different levels as well as reduction of peripheral and central sensitization [55].

Comparison of Botulinum Toxin Treatment and CGRP Treatment

With the introduction of CGRP receptor blockers in 2018 (year of FDA approval), a new chapter has opened in preventive treatment of chronic migraine. Although data from head to head comparative studies between BoNT and CGRP treatment are not available, some known differences are worth mentioning. Most of these differences seem to be in favor of BoNT therapy compared to erenumab, the most commonly used CGRP blocker. Amid good safety profiles for both modes of therapy with only rare serious side effects, the side effect of mild to moderate severity is more common with erenumab. Such side effects as dizziness, nausea, constipation, and reaction at the site of injection are extremely rare with BoNT treatment. Erenumab injections are monthly, whereas BoNT injections are administered every 3–4 months. Medication adherence is relatively low with erenumab (although higher than other antimigraine drugs) [33], but overall adherence is good for BoNT therapy in chronic migraine [47]. Depression associated with chronic migraine, often improves significantly with sustained BoNT therapy [85].

BoNT and CGRP treatment may complement each other as BoNT-A blocks the activity of dural sensory C fibers, whereas CGRP's blocking action is exerted upon A- delta fibers, both contributing to reduction of central sensitivity and pain in migraine. It has been suggested that some patients with severe migraine may benefit from a combination therapy [86]. A recent retrospective chart review study of 257 patients who had been on combination therapy with both BoNTs and erenumab supports this view. In this study, patients experienced a reduction in average headache frequency from 21.5/month to 12.1/month [86]. Furthermore, 5.1% of the patients demonstrated a clinically meaningful improvement in migraine-related disabilities at 6 months, measured by a reduction of 5 points or more in the MIDAS score. Notably, the dropout rate over the 12-month period of treatment was 28% and 3% for CGRP antibody and BoNT therapy, respectively. Botulinum toxin treatment with PREEMPT method, however, has the disadvantage of employing 31 pericranial injection sites that is often uncomfortable for the patients.

Comment

The data from PREEMPT studies and experience of physicians who have treated large numbers of chronic migraine patients with BoNT have established onaA as a very effective agent for treatment of this form of migraine. OnaA treatment improves not only migraine headaches but also its disabling associated mishaps such as poor quality of life and severe depression [85]. The treatment is most effective after administration of repeated doses and maintains its effectiveness and safety over time [62].

The large number of injections (31 sites) endorsed by PREEMPT study is a concern to patients and physicians. It deters some patients with chronic migraine from choosing this effective treatment and also dissuades some patients from continuing treatment. This issue is even more relevant to migraine treatment in pediatric population since children and teenagers are particularly sensitive and reluctant to accept this many pericranial injections. The Walter Reed-Yale technique that employs far fewer injections sites (19 sites) is a good alternative to PREEMPT; in the experience of this author, it results in better participation, comparable results to PREEMPT technique and less dropouts over 5 years of follow up.

Tension-Type Headache (TTH)

Tension-type headache is the most common form of primary headache. Like migraine, it is more common among women. One epidemiological study has found an overall prevalence of 38% (47% among women) [87]. The pain of TTH typically affects the scalp and pericranial muscles, but contraction of neck and jaw muscles is not uncommon. Although the pain is usually not as severe as the pain of migraine,

severe tension headaches do occur and can be quite disabling accounting for loss of work days in 8% to 10% of the affected patients [88]. The most important differential diagnosis is episodic migraine without aura, especially if the associated signs (nausea, photophobia) are subtle. Sinus problems, temporomandibular joint disease, and pain arising from neck pathology (disk degeneration) can also be confused with tension headaches. Harsh family and work environments promote manifestation of TTHs. TTH is more common among individuals with higher levels of education. TTH, like migraine, can be episodic or chronic (headache days 15 or more per month). Chronic TTH is the second most common (after migraine) type of chronic daily headaches and occurs with the same prevalence of 2% (as chronic migraine) in the general population [88].

Pathophysiology

Although stress and psychological factors play a major role in the development of TTH, headache specialists emphasize the contribution of the central nervous system in its pathophysiology, especially in the chronic form.

Diamond and Dalessio [89] proposed the following cascade of events as the pathophysiology of TTH implicating central mechanisms. Local responses in muscle provoke muscle contraction and activate a spinal reflex that polysynaptically activates the thalamic and cortical neurons. This leads to excitation of the descending reticulospinal system that, in turn, causes increased muscle tone and local muscle contraction through the gamma loop–muscle spindles activation. In chronic TTH, perhaps like migraine, both phenomena of peripheral and central sensitization are at work.

Treatment

Episodic TTHs can be treated with aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). Supportive treatment includes behavior modification, psychotherapy, and biofeedback. For chronic tension-type headaches, tricyclic antidepressants (particularly amitriptyline) are the drugs of choice [88]. European guidelines also recommend the use of serotonin and norepinephrine reuptake inhibitors such as venlafaxine and mirtazapine [90].

BoNT Treatment of Tension-Type Headache (TTH)

Eight prospective double-blind, placebo-controlled studies have investigated the efficacy of BoNTs in TTH (Table 5.3). Three studies were class I [90–92], whereas 5 were class II [94–98] according to the efficacy classification of the Assessment

Table 5.3 Double-blind, placebo-controlled studies investigating efficacy of BoNTs in THs

Authors	BoNT	Class	# pts	Dose (units)	POM	Result
Rollnick et al. (2000) [94]	aboA	II	21	200	VAS, HD days	Did not meet POM
Schmidt et al. (2001) [95]	onaA	II	60	20	WHYPI	Did not meet POM
Schulte-Mattler et al. (2004) [91]	aboA	I	60	250	Area under HD curve	Did not meet POM
Padberg et al. (2004) [96]	onaA	II	40	100	VAS, HD days	Did not meet POM
Silberstein et al. (2006) [92]	onaA	I	300	50, 100, 150	Pain-free days	Did not meet POM
Struabe et al. (2008) [93]	aboA	I	120	210, 420	Pain-free days	Did not meet POM
Hamdy and Samir (2008) [97]	onaA	II	28	100	VAS, HD days, QoL	VAS d30: $P = 0.007$
						d90: $P = 0.001$
						QoL: d30: $P = 0.027$
						d90: $P = 0.007$
Harden et al. (2008) [98]	onaA	II	23	100 (25 units/ trigger point)	VAS, HD days	Significant difference in HD frequency, weeks 5–8

VAS visual analog scale, *POM* primary outcome measure, *WHYPI* West Haven-Yale Pain Inventory, *QoL* quality of life, *HD* hydrodistention

and Guidance Subcommittee of the American Academy of Neurology [99]. These controlled studies on TTHs used different outcomes, different techniques of injection and different types of toxins with different doses. Three studies used aboA, whereas 5 used onaA botulinum toxin. Among onaA studies, the injected dose varied from 20 to 150 units. In the aboA groups, the dose varied from 200 to 420 units (Table 5.3). Among these eight studies, two met their primary outcomes (Table 5.3). None of the above-mentioned controlled studies that assessed efficacy of BoNTs in tension headaches used the injection design of PREEMPT studies or doses as high as those used in PREEMPT (155 to 195 units for onaA). However, there are a sizeable number of unblinded studies that report reduction of pain days and pain intensity when botulinum toxins were used for treatment of tension headaches [100].

Comment

The last practice guidelines of the American Academy of Neurology based on data from blinded studies states that botulinum toxins are probably ineffective in treatment of tension headaches [101]. As mentioned in the first edition of this book (2015), this author strongly believes that a multicenter study with a similar design to PREEMPT is needed to assess the true efficacy of BoNT therapy in tension headaches. A comprehensive literature review on this subject published in 2019 from

Johns Hopkins University that looked at the design and doses used in all published studies in this area (including nonblinded investigations) also makes this point [102]. It has been almost 13 years since the last double-blind, placebo-controlled study was published on this subject. Since the PREEMPT study has shown such efficacy and safe profile over time for the use of onaA in chronic migraine, it would be unfair to patients suffering from chronic tension headaches not to conduct a study on the efficacy of BoNT therapy in tension headaches using the PREEMPT design.

Chronic Daily Headaches (CDH)

Chronic daily headaches are defined as headaches that occur 15 or more days per month [103]. A majority of the affected patients have chronic migraine followed by TTHs [104]. The efficacy of BoNTs was investigated in 4 double-blind, placebo-controlled studies [105–108]. One study [108] was based on data from the subgroup of another study [106] on patients with CDH who were on no prophylactic medications. All studies used the mean change of headache free days per month as their primary outcome. The largest study enrolled 702 patients [107]. The first three studies did not meet their primary outcome measure. The subgroup study of Dodick et al. [108], however, demonstrated a significant increase in number of headache free days in the BoNT group compared to the placebo (10.7 days compared to 6.6 days). Based on the aforementioned data, the Therapeutics and Assessment Subcommittee of ANA assigned a level U evidence (insufficient evidence to support or refute efficacy) for BoNT treatment in CDH [101].

Trigeminal Autonomic Cephalalgias (TAC)

This category includes cluster headaches, paroxysmal hemicranias, short-lasting, unilateral neuralgiform headache attacks associated with conjunctival congestion and tearing (SUNCT) and short lasting, unilateral neuralgiform headaches attacks associated with autonomic symptoms (SUNA) [109].

Cluster Headaches

Cluster headache (CH) is a primary headache disorder that affects 0.1% of population [110]. The bouts of pain are usually severe and strictly unilateral and occur in the distribution of the trigeminal nerve over orbital, supraorbital or temporal regions. The attacks last 15 min to 3 h. They can occur from once every 2 days to eight times a day [111, 112]. If the period between attacks is less than 3 months, the condition

is considered as chronic cluster headaches. At least one cranial autonomic symptom is present during the attack including unilateral, conjunctival congestion, nasal stuffiness, and/or running nose. Alcohol consumption, physical exertion, or disturbance of sleep can all trigger acute attacks of CH.

The pathophysiology of cluster headaches involves the trigeminovascular pathway, trigemino-autonomic reflex, and hypothalamus [112]. Neuroimaging studies have shown that the posterior hypothalamus is active during cluster headaches [113]. The paraventricular hypothalamic nucleus probably contributes to cranial autonomic symptoms via its direct connections to the superior salivary nucleus. The suprachiasmatic nucleus of the hypothalamus is known as the primary circadian pacemaker [113] and, hence, is able to contribute to the periodic nature of cluster headaches.

Treatment

Wei and Goadsby [112] discussed in detail the treatment of cluster headaches in a recent review (2021). For acute attacks, treatment consist of subcutaneous sumatriptan (6 mg), high flow oxygen via nonrebreather mask (12 l/min for 15 min), noninvasive vagus nerve stimulation (three, 2-min stimulations), intranasal sumatriptan (20 g), and intranasal zolmitriptan (5 mg or 10 mg). For interim treatment, oral prednisone (30 mg and 100 mg with tapering) and ipsilateral injection of greater occipital nerve with either local anesthetic or steroid is recommended. Preventive treatment includes use of verapamil (360 mg/day), lithium (800–900 mg/day), melatonin (10 mg/day), and topiramate (25–400 mg/day). The category of emerging treatments includes galcanezumab, a CGRP blocker monoclonal antibody (300 mg/day). This drug is now approved by FDA for treatment of episodic cluster headaches based on the statistically significant results from a multicenter, double-blind, placebo-controlled study of 106 patients [114]. However, since in the same study chronic cluster headaches failed to respond to galcanezumab, this drug is not approved by the European Medicines Agency (EMA).

BoNT Treatment of Cluster Headaches

Sostak et al. [115], in an open label study, investigated the effect of 50 units of onaA in 12 patients with refractory cluster headaches. Three of 9 patients with chronic cluster headaches improved significantly. In one of the three, the attacks totally ceased for 18 months. None of the 3 patients with episodic cluster headaches showed any improvement, however.

Lampl et al. conducted an open label study on 17 patients meeting the criteria of the European Federation for chronic cluster headaches [116]. The duration of the study was 28 weeks (4 weeks of preinjection evaluation and 24 weeks of treatment

and observation). OnabotulinumtoxinA (150 units) was injected pericranially using the PREEMPT study approach. After onaA injection, 58.8% of the patients had >50% decrease in the duration of cluster headaches measured in minutes (primary outcome of the study). Another 29.4% demonstrated a 30% to 50% shortening of headache duration in minutes. Mean frequency of headache days also dropped from 28.2 to 11.8 days at week 24 ($P = 0.0001$; 95% CI, 21.33–11.61). Headache Impact Test (HIT-6) showed a mean reduction of 12.7 points ($P = 0.021$).

Aschehoug et al. [117] reported the efficacy of injection of onabotulinumtoxinA into the sphenopalatine ganglion in 7 patients who were followed for 24 months. The injection was performed through a special device introducing 25 to 50 units of the toxin into the ganglion. As a primary outcome, the overall number of CH attacks of any intensity per month was decreased from 57.3 ± 35.6 at the baseline to 12.4 ± 15.2 ($P = 0.018$) at month 18 and to 24.6 ± 19.2 ($P = 0.028$) at month 24. As a secondary outcome, the number of CH attack-free days per month increased from 4.2 ± 5.9 at baseline to 19.1 ± 9.4 ($P = 0.027$) and 12.9 ± 8.8 ($P = 0.018$) in months 18 and 24, respectively. Controlled and blinded studies are necessary to verify these positive results for cluster headaches.

Posttraumatic Headaches (PTH)

Retrospective studies in civilians report a variable prevalence of 30% to 90% headaches after head injury with 18% to 22% lasting beyond 1 year after the head injury [118]. The prevalence of PTH was 38% among soldiers returning from combat with most headaches demonstrating clinical features of migraine [119]; tension headaches were the second most common type. Posttraumatic headaches are usually treated according to the clinical type of the headaches [120]. A brief account on the medical treatment of migraine and tension-type headaches has been addressed earlier in this chapter.

Botulinum Toxin Treatment of Posttraumatic Headaches

The limited literature on treatment of posttraumatic headaches with botulinum toxin-A suggests that this type of headache is also amenable to BoNT treatment.

Yerry et al. [121] evaluated the efficacy of onabotulinumtoxinA in posttraumatic headaches in a real-time, retrospective study. The study group consisted of 64 subjects (63 male) with mostly blast-related injury. Migraine headaches with a frequency of more than 15 days per month were present in 46% of the patients. Patients were injected with onabotulinumtoxinA using the PREEMPT study paradigm and dosage. The patients' response to BoNT treatment was evaluated by the global evaluation of change (GEC)—no difference, better or worse. At the time of closure of the study, headaches improved in 64.1% of the patients, remained unchanged in

28.5%, and worsened in 3.2%. Posttraumatic stress disorder was present in 41.9% of the patients who did not improve with botulinum toxin treatment.

Zirovich et al. [122] conducted a randomized, placebo-controlled, double-blind study in 40 patients with posttraumatic headaches. The mean age of the patients was 34.3 years and 95% of them were male. The head injury was mild but complicated in 38 patients (80%). The study was conducted over 24 weeks. The study design was cross-over with a cross-over at week 16 between toxin and placebo. Patients were injected with abobotulinumtoxinA using a total dose of 387.5 units according to the injection paradigm of the PREEMPT studies (31 injection sites, see PREEMPT technique described earlier in this chapter). The primary outcome was the change in the overall number of headaches per week from baseline. Secondary outcome measures consisted of number of headache days per week and pain severity.
Patients who received BoNT-A demonstrated a significant decrease in the number of headaches per week compared to baseline ($P < 0.001$). The comparative difference of headaches per week was significant when the toxin group was compared with the placebo group (($P = 0.048$). There was a significant decrease in pain severity (measured by VAS) when toxin group was compared with the placebo group ($P = 0.006$). Injection site pain and fleeting paresthesias were the most common side effects occurring with the same frequency in the toxin ad placebo groups. No serious side effects were noted.

Comment

Preliminary results of botulinum toxin injection treatment in cluster and posttraumatic headaches are encouraging. Verification of these positive results awaits conducting multicenter, blinded, and placebo-controlled studies in larger number of patients affected by cluster and posttraumatic headaches.

References

1. Evans RW. Handbook of headache. In: Evans, Mathew, editors. Diagnosis of headaches and medicolegal aspects. Lippincott Wiliams and Wilkins; 2005. p. 1.
2. Headache Classification Committee of the International Headache Society (IHS) the international classification of headache disorders. Cephalalgia. 2018;38:1–211.
3. Lipton RB, Silberstein SD. The role of headache-related disability in migraine management: implications for headache treatment guidelines. Neurology. 2001;56(6 Suppl 1):S35–42. https://doi.org/10.1212/wnl.56.suppl_1.s35.
4. James SL, Abate D, Abate KH, et al. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789–858. https://doi.org/10.1016/S0140-6736(18)32279-7. Erratum in: Lancet. 2019;393(10190):e44

5. Insinga RP, Ng-Mak DS, Hanson ME. Costs associated with outpatient, emergency room and inpatient care for migraine in the USA. Cephalagia. 2011;31:1570–5.
6. Ashkenazi A, Sholtzow M, Shaw JW, Burstein R, Young WB. Identifying cutaneous allodynia in chronic migraine using a practical clinical method. Cephalalgia. 2007;27:111–7.
7. Mathew NT. Pathophysiology of chronic migraine and mode of action of preventive medications. Headache. 2011;51(S2):84–92.
8. Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain. 2000;1238:1703–9.
9. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders. 2nd edn. Cephalalgia. 2004;24(Suppl. 1):9–160.
10. Natoli J, Manack A, Dean B, Butler Q, Turkel CC, Stovner L, Lipton RB. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010;30:599–609.
11. Serrano D, Manack AN, Reed ML, Buse DC, Varon SF, Lipton RB. Cost and predictors of lost productive time in chronic migraine and episodic migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. Value Health. 2013;16:31–8.
12. Lance J, Goadsby P. Mechanism and management of headache. 7th ed. Philadelphia: Elsevier; 2005.
13. Cao Y, Welch KM, Aurora S, Vikingstad EM. Functional MRI-BOLD of visually triggered headache in patients with migraine. Arch Neurol. 1999;56:548–54.
14. Waeber C, Moskowitz M. Therapeutic implications of central and peripheral neurologic mechanisms in migraine. Neurology. 2003;61(suppl 4):S9–S20.
15. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain. 2013;154(Suppl 1):S44–53.
16. Silberstein SD, Dodick DW. Migraine genetics: Part II. Headache. 2013;53(8):1218–29. https://doi.org/10.1111/head.12169.
17. Lafrenière RG, Cader MZ, Poulin JF, Andres-Enguix I, Simoneau M, Gupta N, Boisvert K, Lafrenière F, McLaughlan S, Dubé MP, Marcinkiewicz MM, Amagopalan S, Ansorge O, Brais B, Sequeiros J, Pereira-Monteiro JM, Griffiths LR, Tucker SJ, Ebers G, Rouleau GA. A dominant-negative mutation in the TRESK potassium channel is linked to familial migraine with aura. Nat Med. 2010;16:1157–60.
18. Cernuda-Morollón E, Larrosa D, Ramón C, Vega J, Martínez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology. 2013;81:1191–6.
19. Latif R, Rafique N, Al Asoom L, Alsunni AA, Salem AM, AlNoaimi DA, AlHarbi WM, Shaikh AY, AlRaddadi SA, AlMuhaish LA, Almohazey D, Abdulazeez S, Borgio JF. Diagnostic accuracy of serum calcitonin gene-related peptide and apolipoprotein E in migraine: a preliminary study. Int J Gen Med. 2021;14:851–6. https://doi.org/10.2147/IJGM.S303350.
20. Silberstein SD. Preventive treatment of migraine: an overview. Cephalalgia. 1997;17:67–72.
21. Diener HC, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, Ertas M, Lanteri-Minet M, Reuter U, Sánchez Del Río M, Schoenen J, Schwalen S, van Oene J. TOPMAT-MIG-303 Investigators Group. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2007;6:1054–62.
22. Goadsby PJ, Knight YE. Direct evidence for central sites of action of zolmitriptan (311C90): an autoradiographic study in cat. Cephalalgia. 1997;17:153–8.
23. Hoffmann J, Goadsby PJ. Emerging targets in migraine. CNS Drugs. 2014;28:11–7.
24. Gelfand A, Goadsby PJ. A neurologist's guide to acute migraine therapy in the emergency room. The Neurohospitalist. 2012;2:51–9.
25. Ozkurt B, Cinar O, Cevik E, Acar AY, Arslan D, Eyi EY, Jay L, Yamanel L, Madsen T. Efficacy of high-flow oxygen therapy in all types of headaches. A prospective, randomized, placebo-controlled trial. Am J Emerg Med. 2012;30:1760–4.

26. SibersteinSD. Preventive treatment of migraine: an overview. Cephalalgia. 1997;17:67–72.
27. Goadsby P. Therapeutic prospects for migraine: can paradise be regained? Ann Neurol. 2013;74:423–34.
28. Lanteri-Minet M, Reuter U, Sánchez Del Río M, Schoenen J, Schwalen S, van Oene J. TOPMAT-MIG-303 Investigators Group. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2007;62:1054–62.
29. Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F. The effect of sodium valproate on chronic daily headache and its subgroups. J Headache Pain. 2008;9:37–41.
30. Beran RG, Spira PJ. Levetiracetam in chronic daily headache: a double-blind, randomized placebo-controlled study. (The Australian KEPPRA Headache Trial [AUS-KHT]). Cephalalgia. 2011;31:530–6.
31. Zhang Z, Shu Y, Diao Y, Du Y, Chen L, Liu Y, Du B. Calcitonin gene-related peptide receptor antagonist ubrogepant for the treatment of acute migraine: a meta-analysis. Medicine (Baltimore). 2021;100(8):e24741. https://doi.org/10.1097/MD.0000000000024741.
32. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. A controlled trial of erenumab for episodic migraine. N Engl J Med. 2017;377(22):2123–32. https://doi.org/10.1056/NEJMoa1705848.
33. Talbot J, Stuckey R, Crawford L, Weatherby S, Mullin S. Improvements in pain, medication use and quality of life in onabotulinumtoxinA-resistant chronic migraine patients following erenumab treatment – real world outcomes. J Headache Pain. 2021;22(1):5. https://doi.org/10.1186/s10194-020-01214-2.
34. Silberstein S, Mathew N, Saper J, Jenkins S. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. Headache. 2000;40:445–50.
35. Elkind AH, O'Carroll P, Blumenfeld A, DeGryse R, Dimitrova R. BoNTA-024-026-036 Study Group. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. J Pain. 2006;7:688–96.
36. Saper JR, Mathew NT, Loder EW, DeGryse R, VanDenburgh AM. BoNTA-009 Study Group. A double-blind, randomized, placebo-controlled comparison of botulinum toxin type a injection sites and doses in the prevention of episodic migraine. Pain Med. 2007;8:478–85.
37. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine – a randomized, double-blind, placebo-controlled study. Cephalalgia. 2004;24:838–43.
38. Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70:1707–14.
39. Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. Cephalalgia. 2007;27:492–503.
40. Aurora SK, Gawel M, Brandes JL, Pokta S, Vandenburgh AM. BOTOX North American Episodic Migraine Study Group. Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. Headache. 2007;47:486–99.
41. Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache. 2008;48(2):210–20. https://doi.org/10.1111/j.1526-4610.2007.00949.x.
42. Vo AH, Satori R, Jabbari B, Green J, Killgore WD, Labutta R, Campbell WW. Botulinum toxin type-A in the prevention of migraine: a double-blind controlled trial. Aviat Space Environ Med. 2007;78(5 Suppl):B113–8.

43. Freitag FG, Diamond S, Diamond M, Urban G. Botulinum toxin type A in the treatment of chronic migraine without medication overuse. Headache. 2008;48:201–9.
44. Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, Diener HC, Brin MF. PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010;30:793–803.
45. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, Silberstein SD, Brin MF. PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;30:804–14.
46. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, Diener HC, Brin MF. PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50:921–36.
47. Lipton RB, Varon SF, Grosberg B, McAllister PJ, Freitag F, Aurora SK, Dodick DW, Silberstein SD, Diener HC, DeGryse RE, Nolan ME, Turkel CC. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology. 2011;77(15):1465–72. https://doi.org/10.1212/WNL.0b013e318232ab65.
48. Silberstein SD, Diener HC, Dodick DW, Manack Adams A, DeGryse RE, Lipton RB. The impact of onabotulinumtoxinA vs. placebo on efficacy outcomes in headache day responder and nonresponder patients with chronic migraine. Pain Ther. 2020;9(2):695–707. https://doi.org/10.1007/s40122-020-00199-9.
49. Dodick DW, Silberstein SD, Lipton RB, DeGryse RE, Adams AM, Diener HC. Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: analysis of PREEMPT data. Cephalalgia. 2019;39(8):945–56. https://doi.org/10.1177/0333102418825382.
50. Blumenfeld AM, Silberstein SD, Dodick DW, Aurora SK, Brin MF, Binder WJ. Insights into the functional anatomy behind the PREEMPT injection paradigm: guidance on achieving optimal outcomes. Headache. 2017;57(5):766–77. https://doi.org/10.1111/head.13074.
51. Silberstaien SD. Manual of botulinum toxin therapy. In: Troung, Hallet, Zachary, Dressler, editors. The use of botulinum toxin in management of headache disorder. Cambridge Press; 2013. p. 222–32.
52. Choi YJ, Lee WJ, Lee HJ, Lee KW, Kim HJ, Hu KS. Effective botulinum toxin injection guide for treatment of temporal headache. Toxins (Basel). 2016;8(9):265. https://doi.org/10.3390/toxins8090265.
53. Schaefer SM, Gottschalk CH, Jabbari B. Treatment of chronic migraine with focus on botulinum neurotoxins. Toxins (Basel). 2015;7(7):2615–28. https://doi.org/10.3390/toxins7072615.
54. Richardson D, Jabbari B. Botulinum toxin treatment of chronic migraine. A double blind study with a novel technique employing fewer injections. Poster 124- American Academy of Neurology annual meeting, Vancouver, Canada. April 19, 2016.
55. Ashkenazi A, Blumenfeld A. OnabotulinumtoxinA for the treatment of headache. Headache. 2013;53(Suppl 2):54–61.
56. Zhang X, Strassman AM, Novack V, Brin MF, Burstein R. Extracranial injections of botulinum neurotoxin type A inhibit intracranial meningeal nociceptors' responses to stimulation of TRPV1 and TRPA1 channels: are we getting closer to solving this puzzle? Cephalalgia. 2016;36(9):875–86. https://doi.org/10.1177/0333102416636843.
57. Kara M, Gürçay E, Aydın G, Kaymak B, Sekizkardeş M, Akıncı A, Uludüz D, Özçakar L. Botulinum toxin injections to cranial sutures for chronic migraine rewinding the technique using ultrasound imaging. Toxicon. 2019;25(172):19–22. https://doi.org/10.1016/j.toxicon.2019.10.239.
58. Kim YG, Bae JH, Kim H, Wang SJ, Kim ST. A proposal for botulinum toxin type A injection into the temporal region in chronic migraine headache. Toxins (Basel). 2020;12(4):214. https://doi.org/10.3390/toxins12040214.

59. Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC, Aurora SK, Sirimanne M, DeGryse RE, Turkel CC, Dodick DW. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013;331:48–56.
60. Sandrini G, Perrotta A, Tassorelli C, Torelli P, Brighina F, Sances G, Nappi G. Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. J Headache Pain. 2011;12(4):427–33.
61. Pijpers JA, Kies DA, Louter MA, van Zwet EW, Ferrari MD, Terwindt GM. Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: a double-blind randomized controlled trial. Brain. 2019;142(5):1203–14. https://doi.org/10.1093/brain/awz052.
62. Aurora SK, Dodick DW, Diener HC, DeGryse RE, Turkel CC, Lipton RB, Silberstein SD. 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.
63. Cho ES, Hwang JY, Kim ST. A proposal to prevent the "Mephisto sign" side effect of botulinum toxin type A injection in chronic migraine. Yonsei Med J. 2013;54(6):1542–4. https://doi.org/10.3349/ymj.2013.54.6.1542.
64. Jakubowski M, McAllister PJ, Bajwa ZH, Ward TN, Smith P, Burstein R. Exploding vs. imploding headache in migraine prophylaxis with botulinum toxin A. Pain. 2006;125:286–95.
65. Santana L, Liu C. Experience of botulinum toxin A injections for chronic migraine headaches in a pediatric chronic pain clinic. J Pediatr Pharmacol Ther. 2021;26(2):151–6. https://doi.org/10.5863/1551-6776-26.2.151.
66. Marcelo R, Freund B. The efficacy of botulinum toxin in pediatric chronic migraine: a literature review. J Child Neurol. 2020;35(12):844–51. https://doi.org/10.1177/0883073820931256.
67. Ion I, Renard D, Le Floch A, De Verdal M, Bouly S, Wacongne A, Lozza A, Castelnovo G. Monocentric prospective study into the sustained effect of incobotulinumtoxin A (XEOMIN®) botulinum toxin in chronic refractory migraine. Toxins (Basel). 2018;10(6):221. https://doi.org/10.3390/toxins10060221.
68. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology. 2005;26:785–93.
69. Yuan H, Silberstien S. The use of botulinum toxin in the management of headache disorders. In: Whitcup, Hallett, editors. Handbook of experimental pharmacology. Botulinum toxin therapy; 2021. p. 228–42.
70. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. Pain. 2013; 154(Suppl 1). https://doi.org/10.1016/j.pain.2013.07.021.
71. Greco R, De Icco R, Demartini C, Zanaboni AM, Tumelero E, Sances G, Allena M, Tassorelli C. Plasma levels of CGRP and expression of specific microRNAs in blood cells of episodic and chronic migraine subjects: towards the identification of a panel of peripheral biomarkers of migraine? J Headache Pain. 2020;21(1):122. https://doi.org/10.1186/s10194-020-01189-0.
72. Cernuda-Morollón E, Martínez-Camblor P, Ramón C, Larrosa D, Serrano-Pertierra E, Pascual J. CGRP and VIP levels as predictors of efficacy of Onabotulinumtoxin type A in chronic migraine. Headache. 2014;54(6):987–95. https://doi.org/10.1111/head.12372.
73. Lacković Z, Filipović B, Matak I, Helyes Z. Activity of botulinum toxin type A in cranial dura: implications for treatment of migraine and other headaches. Br J Pharmacol. 2016;173(2):279–91. https://doi.org/10.1111/bph.13366.
74. Matak I, Rossetto O, Lacković Z. Botulinum toxin type A selectivity for certain types of pain is associated with capsaicin-sensitive neurons. Pain. 2014;155(8):1516–26. https://doi.org/10.1016/j.pain.2014.04.027.

75. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459.
76. Lazarov NE. Comparative analysis of the chemical neuroanatomy of the mammalian trigeminal ganglion and mesencephalic trigeminal nucleus. Prog Neurobiol. 2002;66(1):19–59. https://doi.org/10.1016/s0301-0082(01)00021-1.
77. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107:125–33.
78. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155(4):674–84. https://doi.org/10.1016/j.pain.2013.12.009.
79. Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. Toxicon. 2000;38(2):245–58. https://doi.org/10.1016/s0041-0101(99)00153-1.
80. Burstein R, Blumenfeld AM, Silberstein SD, Manack Adams A, Brin MF. Mechanism of action of onabotulinumtoxinA in chronic migraine: a narrative review. Headache. 2020;60(7):1259–72. https://doi.org/10.1111/head.13849.
81. Domínguez C, Vieites-Prado A, Pérez-Mato M, Sobrino T, Rodríguez-Osorio X, López A, Campos F, Martínez F, Castillo J, Leira R. CGRP and PTX3 as predictors of efficacy of onabotulinumtoxin type A in chronic migraine: an observational study. Headache. 2018;58(1):78–87. https://doi.org/10.1111/head.13211.
82. Drinovac V, Bach-Rojecky L, Matak I, Lacković Z. Involvement of μ-opioid receptors in antinociceptive action of botulinum toxin type A. Neuropharmacology. 2013;70:331–7. https://doi.org/10.1016/j.neuropharm.2013.02.011.
83. Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E. Botulinum A toxin effects on rat jaw muscle spindles. Acta Otolarynol. 1993;113:400–4.
84. Weise D, Weise CM, Naumann M. Central effects of botulinum neurotoxin-evidence from human studies. Toxins (Basel). 2019;11(1):21. https://doi.org/10.3390/toxins11010021.
85. Blumenfeld AM, Tepper SJ, Robbins LD, Manack Adams A, Buse DC, Orejudos AD, Silberstein S. Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety. J Neurol Neurosurg Psychiatry. 2019;90(3):353–60. https://doi.org/10.1136/jnnp-2018-319290.
86. Blumenfeld AM, Frishberg BM, Schim JD, Iannone A, Schneider G, Yedigarova L, Manack AA. Real-world evidence for control of chronic migraine patients receiving CGRP monoclonal antibody therapy added to onabotulinumtoxinA: a retrospective chart review. Pain Ther. 2021. https://doi.org/10.1007/s40122-021-00264-x
87. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. JAMA. 1998;279(5):381–3. https://doi.org/10.1001/jama.279.5.381.
88. Freitag F. Managing and treating tension-type headache. Med Clin North Am. 2013;97:281–92.
89. Diamond S, Dalessio DJ. Muscle contraction headache. In: Diamond D, Dalessio DJ, editors. The practicing physician's approach to headache. 4th ed. Baltimore: Williams and Wilkins; 1986. p. 99–113.
90. Bendtsen L, Evers S, Linde M, et al. EFNS guideline on the treatment of tension type headache: report of an EFNS task force. Eur J Neurol. 2010;17:1318–25.
91. Schulte-Mattler WJ, Krack P. BoNTTH Study Group. Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. Pain. 2004;109(1–2):110–4.
92. Silberstein SD, Göbel H, Jensen R, Elkind AH, Degryse R, Walcott JM, Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia. 2006;26:790–800.
93. Straube A, Empl M, Ceballos-Baumann A, Tölle T, Stefenelli U, Pfaffenrath V. Dysport Tension-Type Headache Study Group. Pericranial injection of botulinum toxin type A (Dysport) for tension-type headache – a multicentre, double-blind, randomized, placebo-controlled study. Eur J Neurol. 2008;15:205–13.

94. Rollnik JD, Dengler R. Botulinum toxin (DYSPORT) in tension-type headaches. Acta Neurochir Suppl. 2002;79:123–6.
95. Schmitt WJ, Slowey E, Fravi N, Weber S, Burgunder JM. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. Headache. 2001;41:658–64.
96. Padberg M, de Bruijn SF, de Haan RJ, Tavy DL. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. Cephalalgia. 2004;24:675–80.
97. Hamdy SM, Samir H, El-Sayed M, Adel N, Hasan R. Botulinum toxin: could it be an effective treatment for chronic tension-type headache? J Headache Pain. 2009;10(1):27–34. https://doi.org/10.1007/s10194-008-0082-2.
98. Harden RN, Cottrill J, Gagnon CM, Smitherman TA, Weinland SR, Tann B, Joseph P, Lee TS, Houle TT. Botulinum toxin a in the treatment of chronic tension-type headache with cervical myofascial trigger points: a randomized, double-blind, placebo-controlled pilot study. Headache. 2009;49:732.
99. American Academy of Neurology. Clinical practice guidelines process manual. 2004th ed. St. Paul: The American Academy of Neurology; 2004. Available at: https://www.aan.com/Guidelines/Home/UnderDevelopment. Accessed 1 Aug 2011
100. Wieckiewicz M, Grychowska N, Zietek M, Wieckiewicz G, Smardz J. Evidence to use botulinum toxin injections in tension-type headache management: a systematic review. Toxins (Basel). 2017;9(11):370. https://doi.org/10.3390/toxins9110370.
101. Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, Armstrong MJ, Gloss D, Potrebic S, Jankovic J, Karp BP, Naumann M, So YT, Yablon SA. 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(19):1818–26. https://doi.org/10.1212/WNL.0000000000002560.
102. Freund B, Rao A. Efficacy of botulinum toxin in tension-type headaches: a systematic review of the literature. Pain Pract. 2019;19(5):541–51. https://doi.org/10.1111/papr.12773.
103. Silberstein SD, Lipton RB. Chronic daily headache. Curr Opin Neurol. 2000;13:277–83.
104. Mathew NT, Reuventi U, Perez F. Transformed or evolutive migraine. Headache. 1987;27:102–6.
105. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo- controlled, parallel design study. Cephalalgia. 2004;24:60–5.
106. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. BOTOX CDH Study Group. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized double-blind, placebo-controlled trial. Headache. 2005;45:293–307.
107. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC. BoNTA-039 Study Group. Botulinum toxin type a for the prophylactic treatment of chronic daily headache: a randomized, double blind, placebo controlled trial. Mayo Clin Proc. 2005;80:1126–37.
108. Dodick DW, Mauskop A, Elkind AH, et al. BOTOX CDH Study Group. Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo- controlled study. Headache. 2005;45:315–24.
109. Silberstein SD, Vodovskaia N. Trigeminal autonomic cephalalgias other than cluster headache. Med Clin North Am. 2013;97:321–8.
110. Russell MB. Epidemiology and genetics of cluster headache. Lancet Neurol. 2004;3(5):279–83. https://doi.org/10.1016/S1474-4422(04)00735-5.
111. Headache Classification Committee of the International Headache Society (IHS) the international classification of headache disorders, 3rd edn. Cephalalgia. 2018;38(1):1–211. https://doi.org/10.1177/0333102417738202.
112. Wei DY, Goadsby PJ. Cluster headache pathophysiology – insights from current and emerging treatments. Nat Rev Neurol. 2021. https://doi.org/10.1038/s41582-021-00477-w.

113. May A. Diagnosis and clinical features of trigemino-autonomic headaches. Headache. 2013;53:1470–8.
114. Goadsby PJ, Dodick DW, Leone M, Bardos JN, Oakes TM, Millen BA, Zhou C, Dowsett SA, Aurora SK, Ahn AH, Yang JY, Conley RR, Martinez JM. Trial of Galcanezumab in prevention of episodic cluster headache. N Engl J Med. 2019;381(2):132–41. https://doi.org/10.1056/NEJMoa1813440.
115. Sostak P, Krause P, Förderreuther S, Reinisch V, Straube A. Botulinum toxin type-A therapy in cluster headache: an open study. J Headache Pain. 2007;8:236–41.
116. Lampl C, Rudolph M, Bräutigam E. OnabotulinumtoxinA in the treatment of refractory chronic cluster headache. J Headache Pain. 2018;19(1):45. https://doi.org/10.1186/s10194-018-0874-y.
117. Aschehoug I, Bratbak DF, Tronvik EA. Long-term outcome of patients with intractable chronic cluster headache treated with injection of onabotulinum toxin A toward the Sphenopalatine Ganglion – an observational study. Headache. 2018;58(10):1519–29. https://doi.org/10.1111/head.13398.
118. Theeler B, Lucas S, Riechers RG 2nd, Ruff RL. Post-traumatic headaches in civilians and military personnel: a comparative, clinical review. Headache. 2013;53(6):881–900. https://doi.org/10.1111/head.12123.
119. Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. Headache. 2010;50(8):1262–72. https://doi.org/10.1111/j.1526-4610.2010.01700.x.
120. Dwyer B. Posttraumatic headache. Semin Neurol. 2018;38(6):619–26. https://doi.org/10.1055/s-0038-1673692.
121. 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(3):395–406. https://doi.org/10.1111/head.12495.
122. Zirovich MD, Pangarkar SS, Manh C, Chen L, Vangala S, Elashoff DA, Izuchukwu IS. Botulinum toxin type A for the treatment of post-traumatic headache: a randomized, placebo-controlled, cross-over study. Mil Med. 2020:usaa391. https://doi.org/10.1093/milmed/usaa391.

Chapter 6
Botulinum Neurotoxins and Chronic Low Back Pain

Introduction

Low back pain is anatomically defined as a pain that involves the area(s) between the 12th rib and the iliac crest. It may include nociceptive, neuropathic, and nociplastic (amplified by CNS) qualities [1]. Epidemiological studies have shown that 75% to 80% of all people suffer from low back pain some time during their life time [2]. Among German athletes, Schmidt et al. [3] have reported a 1-year prevalence of 57% and a lifetime prevalence of 66% with the highest lifetime prevalence of 77% noted among volleyball players. The economic burden of low back pain is currently estimated to exceed $100 billion/year in the United States and more than $2.5 billion/year in Australia. Most of this cost seems to be indirect due to the loss of work productivity.

Chronic low back pain is defined as a low back pain that lasts more than 6 months. Chronicity in low back pain is not uncommon. Approximately 60% of the patients with mechanical low back pain are found to have continued low back pain beyond a year after the onset of pain [4].

The anatomy and physiology of human low back pain are complex. All major anatomic elements of the lumbosacral area (skin, muscles, bones, discs, dura, and ligaments) have rich innervation and, when disturbed, are capable of producing low back pain. Direct involvement of neural elements (nerve roots) by compression or inflammation can also cause cLBP. Furthermore, emotional, cognitive, and behavioral elements also contribute to the maintenance of low back pain [5].

Botulinum neurotoxins exert an analgesic effect after subcutaneous or intramuscular injection via peripheral and central mechanisms [6]. In human, they have been shown to alleviate pain in several medical conditions such as chronic migraine, posttraumatic neuropathy, postherpetic neuropathy, and painful diabetic neuropathy [7].

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_6

Anatomy of Low Back Muscles

The lumbosacral area contains a number of muscles arranged at different levels. These muscles stabilize the spine and allow movement of the low back in different directions (flexion, extension, and rotation). Erector spinae (ES) are the most superficial of the low back muscles. At the lumbar region, the ES consist of a single muscle mass with three distinct groups: medially located spinalis, laterally located ileocostalis, and the longissimus which is between these two (Fig. 6.1). The lower fibers of these muscles attach to the sacrum and iliac crest. Rostrally, the three

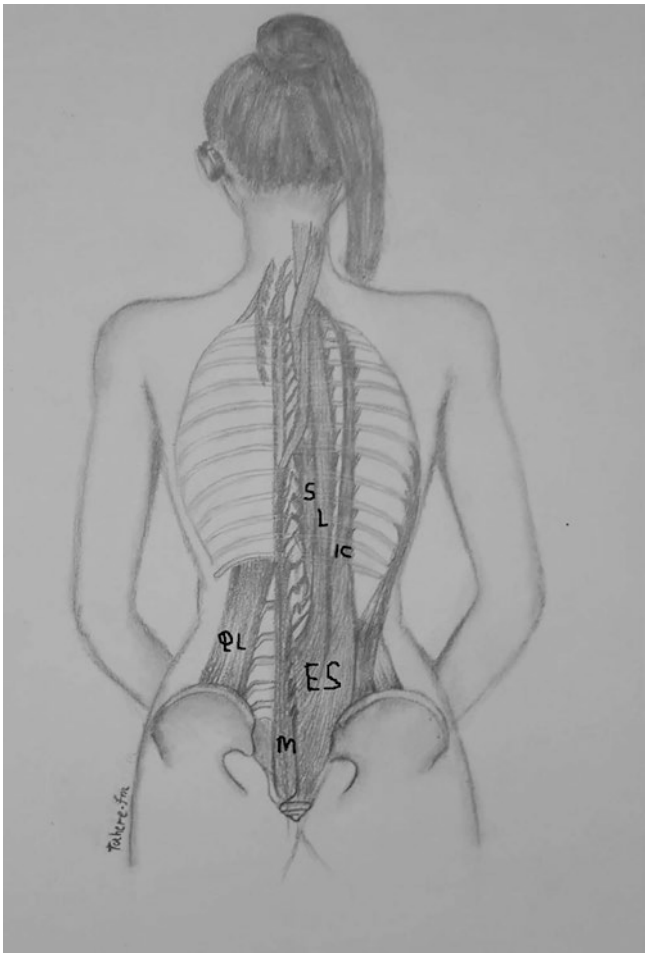

Fig. 6.1 Major muscles of low back: superficial layer (ES, shown on the right) and deep layer; quadratus lumborum (QL) and multifidus (M) shown on the left. The cervicothoracic muscles, spinalis (medial, marked S), longissimus (middle, marked L), and iliocostalis (lateral marked IC) join at L12–L1 level and make a single mass of erector spinae (ES) at the lumbar region

muscles separate from each other approximately at L1/T12 vertebral level. The fibers of ileocostalis attach to T7 to T12 ribs. The fibers of lumbar spinalis and longissimus attach rostrally to the transverse and spinal processes of lumbar and thoracic vertebrae. Unilateral contraction of ES provides lateral flexion and rotation to the opposite side. Bilateral contraction of these muscles extends the spine. The nerves for erector spinae originate from the dorsal division of spinal nerves.

Quadratus lumborum (QL) and multifidus muscles are located deeper than ES muscles (Fig. 6.1). QL is often implicated in low back pain. QL is rostrally attached to the lower level of the 12th rib and the transverse processes of the first four lumbar vertebrae. Its fibers end distally via aponeurosis to the lumbo-inguinal ligaments and attach to the medial part of the iliac crest. Unilateral contraction of QL produces ipsilateral flexion of lumbar spine, whereas bilateral contraction helps with extension of the spinal column. Quadratus lumborum is innervated by the ventral rami of the 12th thoracic and upper three or four lumbar spinal nerves. Its blood supply comes from the lumbar arteries, lumbar branches of iliolumbar artery, and branches of subcostal artery.

Multifidus muscle fills up the groove on either side of the spinal processes of the vertebrae from the sacrum to the coccyx. The multifidus is composed of thin fasciculi which arise from the sacrum (as low as the fourth vertebrae), aponeurosis of the origin of sacrospinalis muscle, posterior medial surface of the ilium, and posterior sacroiliac ligament. In the lumbar region, its fibers attach to mammillary processes of all lumbar vertebrae. Deeper fibers connect to L2–L4 lumbar vertebrae and work to stabilize the joints at each segmental level. At the lower lumbosacral region, more superficial multifidus fibers are close to the skin due to the thinness of the overlying ES in this region. Multifidus muscles, like facet joints, are innervated by the medial branch of the dorsal ramus of the spinal nerves.

Pathophysiology of Chronic Low Back Pain

Pathophysiology of low back pain is complex due to the complexity of low back structures and multiplicity of the causative factors. Recent data have demonstrated that in chronic low back pain, in addition to peripheral elements, chronic pain causes functional changes in thalamocortical loop that promotes pain maintenance [8].

Muscle strain and disturbance play a major role in the pathophysiology of mechanical low back pain. Major low back muscles such as ES and QL are richly innervated. Irritation of nerve endings may lead to accumulation of pain mediators (glutamate, calcitonin gene-related peptide, and substance P) at the periphery causing peripheral sensitization. In patients with an anatomically tight compartment for ES muscles, the compressed muscle can cause pain and discomfort especially during exercise—the lumbar compartment syndrome [9].

Recently, the role of dorsal root ganglia (DRG) in chronic disc disease leading to low back pain has attracted much attention. It has been shown that DRG is very sensitive to pressure and even light compression can cause long periods (5–25 min)

of repetitive firing in DRG neurons [10]. The ruptured disc material, due to proximity to DRG, can influence DRG neurons and upregulate expression of pain mediators and inflammatory agents to produce or enhance pain. In rats, experimental disc puncture at L5–L6 level caused persistent upregulation of calcitonin gene-related peptide (CGRP) in lumbar DRG neurons for the entire 8-week course of the study and a transient (2 weeks) increase in expression of inflammatory agents (Interleukin-6, nerve growth, and tumor necrotizing factors) in DRG [11]. In a similar disc injury experiment in rats, after injury, there is upregulation of tetrodotoxin-sensitive sodium channel (NaV1.7), in L1–L5 DRG neurons. NaV 1.7 channels are associated with sensory transmission in sensory nerves [12]. Disc injury related to injection of Freund's adjuvant into L5 disc results in increased expression of CGRP, Substance P, and nerve growth factor both in DRG and the thalamus lasting for 8 weeks [13]. A sizeable number of DRG neurons that innervate vertebral bodies are also CGRP positive (33% of those innervating L5 vertebra) which suggests a role for CGRP positivity of DRG neurons in bone-generated low back pain [14].

Facet joint disease is another condition often associated with chronic low back pain. Wakai et al. [15] have shown that many DRG neurons have dichotomized axons which project both to facet joints and to low back muscles. These could be the source of referred pain. Approximately 17% of all DRG neurons innervating the facet joints have other axons that extend to the lower back muscles.

The role of sympathetic nervous system in maintaining pain and its chronicity has long been suspected based on anatomical studies showing massive sprouting of sympathetic fibers into DRG after peripheral injury [16]. Normally, no sympathetic fibers are inside DRG, and noradrenergic innervation is present only in the adjacent blood vessels. Following peripheral injury, inflammation develops in DRG and sympathetic ganglia with influx of macrophages and T-cell lymphocytes into DRG. This leads to release of cytokines and increases electrical discharge of DRG neurons. Sympathectomy or removal of sympathetic ganglia decreases the influx of macrophages and T cells into DRG and, consequently, decreases the magnitude of inflammation [17]. Sympathectomy attenuates the excitability of dorsal root ganglion neurons and pain behavior in a lumbar radiculopathy model [18]. In chronic low back pain caused by nerve root or DRG injury, sympathetic nervous system hyperexcitability may play a role in the maintenance of pain (sympathetically maintained pain).

In chronic pain states, peripheral sensitization (PS) due to accumulation of pain mediators and inflammatory agents leads to central sensitization (CS) that is believed to contribute to pain chronicity. This CS occurs at multiple levels of CNS starting with the spinal cord neurons and followed by the brain stem and thalamic and cortical neurons. There is evidence from molecular biology, electrophysiological investigations, and neuroimaging studies that pathological conditions associated with chronic low back pain are capable of inducing central sensitization. In conditions such as herniated disc or trauma, injury leads to generation of ectopic discharges in DRG neurons causing hyperexcitability of spinal cord sensory neurons. Furthermore, light compression of DRG by experimentally induced disc herniation increases evoked responses in the posterior thalamic neurons for a minimum of

40 min [19]. Functional MRI of patients with chronic low back pain compared to asymptomatic age-matched volunteers has shown augmented activation in premotor, supplementary motor, insula, and anterior cingulate cortex in patients with cLBP [20]. Chronic low back pain produces a structural reorganization in sensorimotor cortex, dorsolateral prefrontal cortex, insula, and thalamus [21]. It has been shown that effective treatment of low back pain reverses these deleterious anatomical and functional changes [22].

Medical Treatment of Chronic Low Back Pain

A large number of analgesic agents are available and are frequently used for treatment of chronic low back pain; these include nonsteroidal anti-inflammatory agents (NSAID), tricyclic and tetracyclic antidepressants, muscle relaxants, cyclooxygenase 2 inhibitors, antispasticity agents (tizanidine), anticonvulsants (gabapentin, pregabalin), serotonin/norepinephrine inhibitors (duloxetine), opioid-like agents such as tramadol, strong opioids (oxycodone, oxycontin), and topical anesthetic agents, and, more recently, cannabis. Tricyclic antidepressants are reported to cause a 20% to 40% reduction over placebo in short follow-ups (4–8 weeks), but their long-term effect is not known [23]. The anticholinergic side effects of these agents are also of concern, especially in the elderly. Prospective and control studies with some other agents such as NSAIDs, muscle relaxants, and cyclooxygenase inhibitors have shown marginal improvement over placebo in chronic low back pain [24–29]. In a 12-week study [30], both 200 mg and 300 mg of tramadol moderately improved low back pain compared to placebo ($P = 0.052$ and $P = 0.009$); the disability index, sleep quality, and patient assessment score also improved as secondary measures ($P = 0.012$). Topical NSAID diclofenac has shown some promise in reducing osteoarthritic pain, but systematic studies in chronic low back pain are lacking. In acute and subacute low back pain, one prospective, open-label study has suggested efficacy of lidocaine patch to improve pain and quality of life, and these positive effects were associated with high scores in patient satisfaction [31]. However, controlled studies in chronic low back pain with lidocaine patch are not available [32]. The Cochrane Review of literature on the effect of opioids on pain and function among patients with low back pain encompassed 15 blinded studies with a total of 5600 patients during the period of 2007 to 2012 [33]. Both tramadol (weak opioid function) and strong opioids improved chronic low back pain and function over placebo (moderate for pain, mild for function). Two studies found a comparable effect in chronic low back pain for opioids with tricyclic antidepressants. None of the studies addressed the long-term efficacy and safety. Long-term use of opioids is confounded by development of addictive behavior.

In a comprehensive review of treatment options for chronic low back pain [34], authors recommended tricyclic antidepressants (nortriptyline, 25–150 mg daily), tramadol ER (100–300 mg daily), and lidocaine patch (5%, 1–3 patches applied topically for up to 12 h) as the first line of medical treatment. In view of limited

supportive literature, the long-term efficacy of tramadol ER and lidocaine patch in treatment of cLBP is not well established. Despite medical therapy, most patients with chronic low back pain continue to experience pain and are not satisfied with their level of pain management.

Physical therapy (PT) is aimed to reduce pain, and therapists can educate patients to perform passive and active movements that potentially may prevent progression of low back pain and disability. While PT is commonly used in management of cLBP, well-designed studies are scant; furthermore, methodological problems and paucity of high-quality investigations prevent drawing conclusions regarding the precise efficacy of physical therapy [35, 36].

Massage, heat, and cold applications are temporarily effective for pain, but show no long-term benefits. The few available high-quality studies advocate that spinal manipulative therapy (SMT) has no advantage in management of chronic low back pain [37]. A review of studies (10 randomized clinical trials) using yoga for management of chronic low back pain suggested strong evidence for short-term and long-term effect on pain and moderate effect on pain-related disability [38]. However, a recent review of RCTs on Yoga and mindful practices emphasized shortcoming of reported studies including small number of patients and difficulty with blinding the study [39].

Transcutaneous electrical nerve stimulation (TENS) has been found to be ineffective based on two negative high-quality studies [40]. Acupuncture data in low back pain are hard to interpret due to heterogeneity of participants and suboptimal quality of most studies; improvements in pain and function are reported in some controlled studies, but the effects are transient [41]. One review concluded that ultrasound treatment has no appreciable effect on pain or functionality [42], whereas a recent one claims that five of six studies have shown a positive effect on nonspecific chronic low back pain [43]. There are no convincing data on the value of transcortical electrical and magnetic cortical stimulation in chronic low back pain [44].

Epidural injections with anesthetic agents (with or without steroids) improve pain flairs in cLBP, but the effects are generally transient. A review of the literature on this subject found 15 blinded, placebo-controlled studies with the best results reported for radiculopathies due to disc herniation and spinal stenosis [45]. Bone loss as well as a potential for bone fracture have been reported after epidural injection of steroids [46].

Surgical treatment of low back pain has produced mixed results. Spinal fusion alleviates pain and improves function in patients with degenerative spine disease, but the positive effects may not last long. Minimal spinal surgery without open surgery in selected patients has produced good short-term results. Longer observations are needed, however [47].

A Cochrane Review of 6 high-quality publications provided strong evidence that behavioral therapy had a moderate effect in decreasing pain, but no noticeable effect on patients' functional status or behavioral health. The review concluded that both the type of patients that benefit from behavioral therapy and the type of behavioral therapy which is most effective still need to be determined [48]. Cannabis may be helpful in chronic low back pain because of its proven analgesic effect, alleviating

fear of pain as well as excellent safety profile, but high-quality clinical trials investigating its role in cLBP are not yet available [49].

Evidence for Efficacy of BoNTs in Chronic Low Back Pain

A Medline search identified five randomized, placebo-controlled, blinded studies that have investigated the efficacy of BoNT therapy in chronic low back pain [50–54] and one prospective study with long-term follow-up (Table 6.1) [55]. Four of the above-mentioned six studies [50, 52, 54, 56] that injected the toxin into the erector spinae muscle at 5 lumbar levels and used comparable toxin dosage reported significant improvement of chronic low back pain. One study that employed the same injection methodology, but lower dose of the toxin failed to improve cLBP [53]. One other study in which investigators injected quadratus lumborum and iliopsoas muscles also reported negative results [51]. None of the patients injected into erector spinae muscles, even with relatively high doses of BoNT (400 units in case of bilateral injections) reported any serious side effects such as weakness of the legs or impaired balance.

Studies

Foster et al. (2001) [50]
This first blinded and placebo-controlled study of BoNT in chronic low back pain was reported by our group looking at an active duty and retired military population at Walter Reed Army Medical Center in Washington DC. We studied 31 subjects with unilateral cLBP randomized into the BoNT group (15 patients) and placebo group (16 patients). The study had a parallel design. The inclusion criteria consisted of LBP of more than six-month duration, unilateral or predominately unilateral LBP (severity level of 4 or more at visual analog scale—VAS), and failure to respond to at least two major analgesic medications. All patients were adults, 18 years or older. The exclusion criteria consisted of known hypersensitivity to onabotulinumtoxinA (onaA), pregnancy or planned pregnancy, presence of neuromuscular junction disorders, being on medications known to cause significant neuromuscular junction dysfunction, MRI evidence of acute low back pathology requiring surgery, history of previous back surgery, and history of corticosteroid injections to the lumbosacral area within 12 weeks of enrollment. Patients who were involved in litigation, seeking significant disability for low back pain, or with evidence of secondary gain were also excluded. The mean age of the study group was 46.4 years for onaA group and 47 years for the control group (range, 20–73). The mean duration of pain was 8.1 years for the BoNT-A group and 5.7 years for the control group (range 6 months to 30 years). Patients were instructed to continue their analgesic medications during the study but not to change the dose, while avoiding new analgesic medications.

Table 6.1 Blinded studies reporting on the effect of BoNT therapy in chronic low back pain

Authors and date	Study type and class	# Patients	Type of toxin	Dose in units	Site of injection	Primary outcome	Results
Foster et al. (2001) [50]	DB, PC, PD, class II	31	onaA	200 u, 40 u per each lumbar level	Unilateral injection, erector spinae, lumbar region	VAS 50% decrease and OLBPQ	Both at 3 and 8 weeks, VAS and OLBPQ scores improved significantly in favor of onaA *P* values: 0.012, 0.009, and 0.011, respectively.
De Andres et al. (2010) [51]	DB, PC, PD, class II	28	onaA	In one side 50 u of onaA, on the other side either saline or bupivacaine	Iliopsoas and quadratus lumborum, each 50 u, same volume with other agents	Difference in VAS at 15, 30, and 90 days. Different questionnaires for ADL, anxiety, and depression ….	Trend toward significance in onaA group as to VAS change but $P > 0.05$
Cogne et al. (2017) [53]	DB, PC, PD, class II	19	onaA	200 u, 20 u per each lumbar level	Bilateral injection, erector spinae, lumbar region	VAS, QBPDS, PGIC	No significant improvement in any measures.
Machado et al. (2011) [52]	DB, CO, class II	37	aboA	40 u per lumbar level. Total dose: 500 u for unilateral and 1000 u for bilateral injection	Unilateral and bilateral, erector spinae, lumbar	Vas, OLBPQ, PGIC	At week 4, VAS score change favored onaA ($P = 0.008$). In toxin group, significant change in OLBPQ and PGIC ($P = 0.0448$ and $P = 0.0293$)

(continued)

Table 6.1 (continued)

Authors and date	Study type and class	# Patients	Type of toxin	Dose in units	Site of injection	Primary outcome	Results
Jazayeri et al. (2018) [54]	SB, PD, class II	50	aboA	40 u/lumbar level	Erector spinae, lumbar	VAS, OLBPQ	At 4 and 8 weeks, VAS and OLBPQ scores favored aboA ($P < 0.05$, <0.01, and < 0.05, respectively)

DB double-blind, *SB* single-blind, *PO* Placebo-controlled, *PD* Parallel design, *CO* cross-over design, *VAS* Visual Analog Scale, *OLBPQ* Oswestry Low Back Pain Questionnaire, *PGIC* Patient Global Impression of change, *onaA* onabotulinumtoxinA (Botox), *aboA* abobotulinumtoxinA (Dysport)

They were also instructed to make no changes in their physical therapy regimen as prescribed by their treating physician.

In the BoNT group, each patient received a total of 200 units of onaA into the erector spinae (ES) on the side of unilateral or predominately unilateral pain. The ES muscle was injected at 5 points: L1, L2, L3, L4, and L5 levels, 40 units per level regardless of the pain location within any of these 5 levels (Fig. 6.2).

The dilution used was 100 units/cc. The baseline level of pain and degree of disability were documented by using the visual analog scale (VAS) and the Oswestry Low Back Pain Questionnaire (OLBPQ). Evaluations were performed at baseline and at 3 and 8 weeks using the VAS score, and at baseline and 8 weeks using the OLBPQ score. The primary outcome measure was 50% or more reduction in pain as defined by VAS at 8 weeks.

At 3 weeks, 11 of 15 subjects (73.3%) who had received onaA had >50% pain relief versus 4 of 16 (25%) in the control group ($P = 0.012$). At 8 weeks, 9 of 15 (60%) subjects in the onaA group and 2 of 16 (12.5%) in the control group expressed relief ($P = 0.009$). A repeat OLBPQ at 8 weeks showed significant improvement of quality of life in 10 of 15 (66.7%) patients in the BoNT group versus 3 of 16 (18.8%) in the control group ($P = 0.011$). None of the patients experienced any significant side effects. It was concluded that paraspinal administration of onabotulinumtoxinA at 5 lumbar levels into ES is safe and can relieve pain and improve the quality of life in patients with predominantly unilateral chronic low back pain without a history of surgery or evidence of acute back pathology on MRI.

Jabbari et al. (2006) [55]

In this prospective, open-label study, we investigated the effect of repeated injections of onabotulinumtoxinA in patients with chronic low back pain over 16 months. The cohort consisted of 75 patients with chronic LBP refractory to medical or surgical treatment. The inclusion and exclusion criteria were the same as those of our

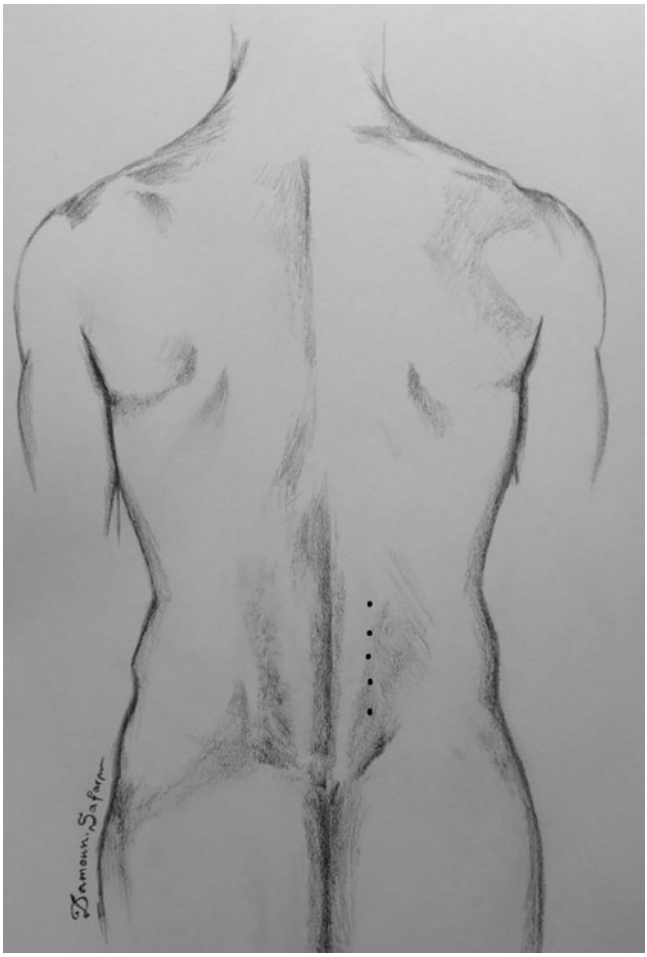

Fig. 6.2 Recommended sites of BoNT injection into the erector spinae muscles for chronic low back pain [50]

previous blinded study described above [55] with the exception of including patients with bilateral low back pain. The dose and technique were also similar to our blinded study, with a minor modification (an extra dose of 10 to 20 units was administered more laterally into the bulk of the erector muscles at the level of most discomfort). The patients had a mean age of 46.1 years (range 21–79) and mean pain duration of 9.2 years (range 7 months to 50 years). Of the 75 patients, 21 were female, and 84% of the studied cohort had bilateral low back pain. Other factors noted among the cohort included previous back surgery ($n = 14$), root pain ($n = 20$), epidural steroids injections ($n = 19$), and narcotic analgesic use ($n = 36$). None had back surgery or steroid injections within 6 months of enrollment. Magnetic resonance imaging (MRI) showed a variety of low back pathologies (50%), but none were severe or

acute enough to require surgical intervention. The most common pathologies consisted of chronic degeneration of the spine, canal stenosis, and chronic disc protrusions. Patients were instructed not to change their analgesic medications and continue with their physical therapy during the course of the study. Pain intensity (VAS), pain frequency (pain days measured in the pain impact questionnaire (PIQ)), Oswestry low back pain questionnaire (OLBPQ), and patient level of satisfaction were assessed at baseline, 3 weeks, and at 2, 4, 6, 8, 10, 12, and 14 months. OnaA was injected into the paraspinal muscles at five levels (between L1 and S1) unilaterally or bilaterally depending on individual patient's pattern of pain. The dose per site was 40 units with exceptional patients receiving an additional 10–20 units at one level (more laterally) if the local area of pain extended laterally. The total dose per session ranged from 200 to 500 units. Reinjections were performed at 3 to 5 months if pain returned; most patients had reinjections every 4 months.

At 3 weeks, 40 patients (53%) and at 2 months, 39 patients (52%) reported significant pain relief. The change in mean VAS, mean OLBPQ, and mean PIQ was significant compared to the baseline at 2 months after each injection period ($P < 0.005$) compared to baseline and remained so over subsequent treatments. Among initial responders, 91% continued to respond over the length of the study (Fig. 6.3).

Nine of 20 patients (45%) with root pain reported diminished root pain after treatment. After the first treatment, three patients (4%) had mild-flu-like symptoms which lasted 2 to 5 days. No other side effects were noted.

De Andres et al. (2010) [51]

The authors enrolled a total of 28 patients (20 females) with chronic bilateral myofascial pain in the low back region. All patients had distinct trigger points which upon pressure evoked referred pain. The involved muscle distribution was as follows: psoas (18.5%), quadratus lumborum (18.5%), and psoas plus quadratus

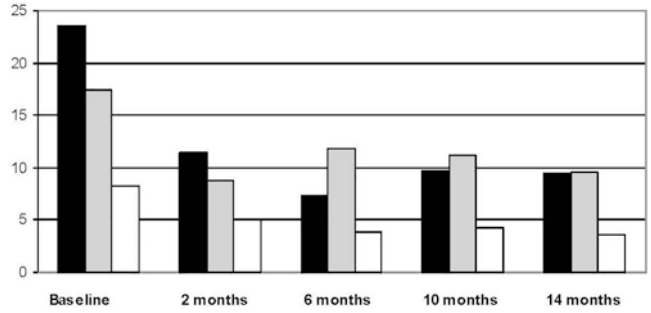

Fig. 6.3 Open-label study of onaA in cLBP with 16-months follow-up. The values of mean pain days assessed by Pain Impact Questionnaire (PIQ), Oswestry low back pain questionnaire (OLBPQ), and visual analog scale (VAS) are represented by black, gray, and white colors, respectively. Injections were performed at baseline months 4, 8, and 12 (2 months before represented values). (From Jabbari et al. 2006 [55] in Pain Medicine. Reprinted with permission from publisher (Oxford Academic))

lumborum (63%). The study was designed to evaluate prospectively and blindly the efficacy of onabotulinumtoxinA versus saline or bupivacaine. Twenty-seven patients completed the study. All patients received onaA injections into quadratus lumborum and iliopsoas (IS) muscles on one side. On the contralateral side, 13 patients received bupivacaine (0.25%), and 14 subjects received saline. The injected onaA solution was 100 units/cc. Each muscle (QL or IS) received 50 units, fluoroscopically injected deep into the muscle.

The inclusion criteria were as follows: Mechanical low back pain longer than 6 months duration, age 20–70, existence of bilateral trigger points with associated referred pain in the iliopsoas muscle, quadratus lumborum muscle, or both, and no response to conservative medical and physical therapy. Patients with previous back surgery, spondylolisthesis, facet joints arthropathy, known or suspected hypersensitivity to BoNTs, neurologic deficits in the painful area, neuromuscular junction or motor neuron diseases, diagnosis of fibromyalgia, and pre-existing inflammation or infection of the injection sites were excluded.

The primary outcome was the difference between VAS score on the side of BoNT injection and the side of saline or bupivacaine injection at 15, 30, and 90 days. The authors used five different questionnaires (Hospital Anxiety and Depression scale, Lattinen, Oswestry, and Spielberger State-Trait Anxiety Index) to evaluate the effects of treatment on daily life activities and psychologic status of the patients.

OnaA administration did not significantly reduce VAS scores compared with contralateral saline or bupivacaine injections. Nonetheless, the authors reported a trend toward significance that was seen only in the BoNT group in respect to VAS score. The authors concluded that administration of onaA provided several subjects significant pain relief, but cautioned against its cost in clinical practice.

Machado et al. (2011) [52]

This double-blind, placebo-controlled, parallel design study conducted at Yale University, New Haven, CT, was technically modeled after the study of Foster et al. [50] to evaluate the efficacy of abobotulinumtoxinA (aboA) in patients with chronic low back pain. A total of 90 subjects were enrolled allowing for 12% dropout. The inclusion criteria consisted of age over 18 years, unilateral or bilateral chronic (>6 months) low back pain, failure to respond to at least two pain medications, and a pain level of >4 in VAS. Subjects with a history of prior back surgery or steroid injections within 6 months prior to enrollment were also excluded. AboA was injected into the erector spinae muscles unilaterally or bilaterally depending on the patients' pain pattern and at 5 lumbar levels. The total dose per side was 500 units (which approximated the 200 units of onaA used in the Foster et al.'s study). The dose per level was 100 units. The primary outcome of the study was the proportion of patients with VAS < 4 in aboA group compared to placebo group at weeks 4 and 6. Other efficacy measures consisted of American Chronic Pain Association (ACPA) quality of life scale, the Oswestry low back pain disability questionnaire (OLBPQ), the short form SF-32, and patient global impression of change (PGIC). Evaluations were done at 4, 6, 8, 12, and 16 weeks after aboA/saline injections.

At week 4, 7 of 18, patients in the aboA group and 4 of 19 patients in the placebo group showed the desired VAS improvements ($P < 0.0084$). At week 6, 9 of 18 patients in the toxin group and 4 of 19 patients in the placebo group showed the defined VAS improvement ($P < 0.0911$). Functionality and quality of life as measured by OLBPQ improved in 10 of 18 and 4 of 19 patients in toxin and placebo groups, respectively ($P = 0.0448$). Eight of 18 patients in the toxin group and 2 of 19 patients in the placebo group described their pain as much improved as measured by PGIC ($P = 0.0293$). There were no serious side effects. Three patients in the toxin group and two patients in the placebo group developed pain at the site of injection that lasted for 2 to 3 days ($P = 0.6390$). Improvement of quality of life on ACPA scale occurred in five patients of the aboA group and one of the patients in the placebo group ($P = 0.0897$). The authors concluded that in patients with chronic low back pain, injection of aboA into the erector spinae muscles improves pain, function as well as the patient's satisfaction with treatment. A multicenter study using a similar technique and dose in a larger number of patients was recommended.

Cogne et al. (2017) [53]
This study was randomized, double-blind, placebo-controlled with a cross-over design. The studied subjects had chronic low back pain with a duration exceeding 6 months. Inclusion and exclusion criteria were similar to that described in the aforementioned studies. The patients' physical therapy program continued during the study. No patient was allowed to take opioids. The primary outcome measure was a change of 40 mm in visual analog scale (0–100 mm), 30 days after injection. Secondary measures were several, among them: Quebec pain disability scale, patient satisfaction with treatment, Schober and Master test for spinal mobility, and ability to work. Nineteen patients were studied: 9 received the toxin, and 10 received placebo. Injections were bilateral into paravertebral muscles, at 5 lumbar levels on each side. The total dose of toxin (onabotulinumtoxinA) was 200 units, 100 units for each side, 20 units/site. For the placebo group, a similar volume of saline (4 cc) was used. The authors found no difference between onaA and placebo regarding any of the primary or secondary measures. They stated that the failure of onaA to improve their patients' low back pain might have been related to the lower dose of the toxin (20 u instead of 40 u per lumbar level) used in their study compared to the study of Foster et al. [50]. They also mentioned the small number of patients as a limitation of their study.

Jazayeri et al. (2019) [54]
The authors assessed the efficacy of abobotulinumA (aboA-Dysport) in chronic low back pain through a randomized, placebo-controlled, single-blind study. The criterion for inclusion into the study was low back pain exceeding 6 months in duration and age of older than 18 years. Efficacy measures consisted of VAS for pain and OLBPQ for function. Fifty patients participated in the study, 25 in each group (toxin and saline). In the toxin group, 40 units of aboA were injected into each lumbar level into the paraspinal muscles. At week 4, 19 of 25 patients (76%) in the aboA group showed VAS improvement versus 5 of 25 (20%) in the saline group ($P < 0.05$).

At 8 weeks, the VAS change was again in favor of aboA ($P < 0.011$). Functional improvement at week 8 was also statistically significant in favor of aboA ($P < 0005$). No patient developed any serious side effects. The authors concluded that paraspinal injection of aboA is safe and effective in treatment of cLBP.

Case Report

A 57-year-old Caucasian male suffered from chronic low back pain for 10 years. The pain began insidiously, gradually increased in intensity, and became daily over the past 2 years. The pain concentrated in the lower lumbar region. He described no radicular pain. Episodes of severe exacerbations were frequent and disabling. When severe, the pain intensity was rated as 10 out of 10 on VAS. He used a large number of analgesic medications over years with no relief. His current pain medications consisted of gabapentin (800 mg, three times daily) and Cymbalta (90 mg, daily). In addition, he was taking oxcarbazepine (600 mg, twice daily) and lamotrigine (200 mg, twice daily) for depression. He denied to have had back surgery in the past or using epidural steroid injections. The neurological examination was normal. A magnetic resonance imaging (MRI) of the lumbosacral spine showed mild degenerative changes, but no acute pathology.

AbobotulinumtoxinA (aboA—Dysport), 500 units (100 units per each lumbar level), was injected into the erector spinae muscles under EMG guidance. The patient was evaluated monthly with VAS and patient global impression of change (PGIC). Two weeks after the initial treatment, he reported absence of low back pain. VAS scores at months 1, 2, 3, and 4 were at 0, 1, 1, and 2 levels, respectively. At 4 months, he reported his experience with aboA treatment as very satisfactory. There were no side effects associated with aboA treatment.

During the years 2004–2015, when I was in charge of Yale University's botulinum toxin treatment program, I have followed several patients with cLBP that have experienced good results for years after repeated injections of onaA or aboA into ES muscles. The injection protocol was the one originally designed by us at Walter Reed Army Medical Center [50] and proved effective in later studies [52, 54, 55].

How Does the Administration of Botulinum Toxin Improve Low Back Pain?

The exact mode of action of botulinum toxin-A in chronic low back pain still remains to be determined. Based on animal and human research data, several plausible mechanisms exist:

1. In muscles, both A and B toxins produce relaxation via inhibiting the release of acetylcholine in the neuromuscular junction. This could explain some of the pain

relief especially when low back pain is associated with muscle tightness and spasms. Furthermore, decreased muscle tone is often associated with a reduction in muscle bulk (atrophy). This decrease in muscle bulk (especially in the ES muscle) may be helpful when back pain is attributed to anatomically tight compartment (lumbar compartment syndrome) [56].

2. As described under pathophysiology of cLBP, many causes of low back pain, especially protruded disc, produce marked accumulation of pain mediators (CGRP, substance P) and inflammatory agents (cytokines) in DRG causing its hyperexcitability and leading to peripheral sensitization (PS). In animal studies, peripherally injected rimabotulinumtoxinB blocks release of substance P from DRG and dorsal horn neurons and reduces dorsal horn neuronal activation (c-fos) evoked by formalin injection [57]. Furthermore, local trauma and ruptured disc initiate local accumulation of glutamate, a potent pain mediator, which also can enhance PS [58]. In the formalin model of pain, pretreatment of rat's paw with local administration of onaA (a week before formalin injection) significantly reduces local accumulation of glutamate and local inflammation relieving the pain related to formalin application [59]. In human, injection of 5 units of onaA into the temporalis muscle following introduction of 0.2 cc/1 mol of glutamate markedly reduces glutamate-generated pain within hours of administration [60].
3. It has been shown that both development of inflammation in DRG and increased pain mediators within it are enhanced by extensive sprouting of sympathetic fibers into DRG after peripheral nerve injury [16] and sympathectomy or removal of sympathetic ganglia can reduce accumulation of inflammatory agents and pain mediators in DRG caused by disc protrusion [17]. In this regard, Rand and Whaler [61] have shown that peripheral injection of onabotulinumtoxinA impairs sympathetic transmission and, hence, has the potential to reduce pain mediators and inflammatory agents.
4. The aforementioned effects of BoNTs can all reduce central sensitization (CS) via reducing peripheral sensitization (PS). Moreover, intramuscular administration of onaA may reduce central sensitization via its suppressing effect on muscle spindle discharge [62]. Muscle spindles are one of the major sources of nonnociceptive input to the central nervous system reporting muscle length to CNS. In chronic pain disorders with established CS, wide-range function spinal cord neurons can perceive nonnociceptive stimuli as nociceptive [63]. Reducing the input from muscle spindles can reduce central sensitization.
5. Reduction of central sensitization in chronic pain disorders can also result from the central effect of peripherally injected botulinum toxins as has been suggested by recent evidence from a number of animal studies [6].
6. Relevant to our injection technique [50, 52, 55], it is possible that some of the analgesic effects of BoNT-A injections in cLBP result from spreading the relatively high dose of the toxin used in these studies beyond the confines of the lumbar erector spinae muscles. A posterior spread would get some of the toxin into the space between the posterior margin of the ES muscles and the vertebral bodies directly in contact with posterior sensory rami in the lumbar region. A

technique recently developed in anesthesiology and called erector spinae block introduces anesthetic agents into this space for avoiding perisurgical pain [64]. Limited studies have shown the utility of this technique in alleviating chronic low back pain [65].

Comment

Chronic low back pain is a complex disorder with heterogeneous causes and still poorly understood pathophysiology. Our two blinded [50, 52] and one open-label 16-month study [55] have shown the utility of erector spinae injections (at 5 lumbar levels) in chronic low back pain. It should be emphasized that the cohorts of these studies did not have acute lesions in MRI or history of previous spinal surgery (failed back). Although we were worried about possible weakening effects of the relatively high doses of onaA and aboA used in these studies, none of the patients in the above-mentioned three studies complained of muscle weakness or impaired ambulation. This may be due to the size of lumbar erector spinae and participation of other muscles and tendons in keeping the stability of spine. Nonetheless, in the case of very thin patients, a reduction of the dose is advisable until the safe dose for fragile individuals can be established through the results of large multicenter studies.

The Assessment and Guideline subcommittee of the American Academy of Neurology in 2008 rated the efficacy of onabotulinumtoxinA for treatment of low back, as level C (possibly effective) due to availability of one class II study [50] at that time [66]. With the publication of the Yale study [52] (another class II study) in 2016, the same level of efficacy (possibly effective C level) could be applied to the use of abobotulinumtoxinA in chronic low back pain. The study of De Andres et al. [51] that failed used a different set of muscles, i.e., iliopsoas and quadratus lumborum rather than erector spinae. In the study of Cogne et al. [53] which used the same technique of our successful studies [50, 52, 55], failure to reach statistical significance, as the authors commented was most likely due to using a considerably lower toxin dose (approximately half of what was used).

In view of this author, it is now time to conduct a large multicenter study of chronic low back pain using the dose and design of the already successful reported methodology (injection into erector spinae with relatively high doses of BoNT-A) [50, 52]. Such a study, because of the size of the study cohort, could define the efficacy of BoNT injection into ES in different etiological subgroups of patients with chronic low back pain.

References

1. Knezevic NN, Candido KD, Vlaeyen JWS, Van Zundert J, Cohen SP. Low back pain. Lancet. 2021;8:S0140-6736(21)00733-9. https://doi.org/10.1016/S0140-6736(21)00733-9.

2. Andersson GBJ. Epidemiological features of chronic low-back pain. Lancet. 1999;354:581–5.
3. Schmidt CP, Zwingenberger S, Walther A, Reuter U, Kasten P, Seifert J, Günther KP, Stiehler M. Prevalence of low back pain in adolescent athletes – an epidemiological investigation. Int J Sports Med. 2014;35(8):684–9. https://doi.org/10.1055/s-0033-1358731.
4. Itz CJ, Geurts JW, van Kleef M, Nelemans P. Clinical course of non-specific low back pain: a systematic review of prospective cohort studies set in primary care. Eur J Pain. 2013;17(1):5–15. https://doi.org/10.1002/j.1532-2149.2012.00170.x.
5. Vlaeyen JWS, Crombez G. Behavioral conceptualization and treatment of chronic pain. Annu Rev Clin Psychol. 2020;16:187–212. https://doi.org/10.1146/annurev-clinpsy-050718-095744.
6. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459.
7. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes – an evidence based review. Toxicon. 2018;147:120–8. https://doi.org/10.1016/j.toxicon.2018.01.017.
8. Tu Y, Fu Z, Mao C, Falahpour M, Gollub RL, Park J, Wilson G, Napadow V, Gerber J, Chan ST, Edwards RR, Kaptchuk TJ, Liu T, Calhoun V, Rosen B, Kong J. Distinct thalamocortical network dynamics are associated with the pathophysiology of chronic low back pain. Nat Commun. 2020;11(1):3948. https://doi.org/10.1038/s41467-020-17788-z. Erratum in: Nat Commun. 2020, 11(1):4347
9. Nathan ST, Roberts CS, Deliberato D, Nathan ST, Roberts CS, Deliberato D. Lumbar paraspinal compartment syndrome. Int Orthop. 2012;36:1221–7.
10. Howe JF, Loeser JD, Calvin WH. Mechanosensitivity of dorsal root ganglia and chronically injured axons: a physiological basis for the radicular pain of nerve root compression. Pain. 1977;3:25–41.
11. Miyagi M, Ishikawa T, Orita S, Eguchi Y, Kamoda H, Arai G, Suzuki M, Inoue G, Aoki Y, Toyone T, Takahashi K, Ohtori S. Disk injury in rats produces persistent increases in pain-related neuropeptides in dorsal root ganglia and spinal cord glia but only transient increases in inflammatory mediators: pathomechanism of chronic diskogenic low back pain. Spine (Phila Pa 1976). 2011;36:2260–6.
12. Sadamasu A, Sakuma Y, Suzuki M, Orita S, Yamauchi K, Inoue G, Aoki Y, Ishikawa T, Miyagi M, Kamoda H, Kubota G, Oikawa Y, Inage K, Sainoh T, Sato J, Nakamura J, Toyone T, Takahashi K, Ohtori S. Upregulation of NaV1.7 in dorsal root ganglia after intervertebral disc injury in rats. Spine (Phila Pa 1976). 2014;39:E421-6.
13. Jung WW, Kim HS, Shon JR, Lee M, Lee SH, Sul D, Na HS, Kim JH, Kim BJ. Intervertebral disc degeneration-induced expression of pain-related molecules:glial cell-derived neurotropic factor as a key factor. J Neurosurg Anesthesiol. 2011;23:329–34.
14. Ohtori S, Inoue G, Koshi T, Ito T, Yamashita M, Yamauchi K, Suzuki M, Doya H, Moriya H, Takahashi Y, Takahashi K. Characteristics of sensory dorsal root ganglia neurons innervating the lumbar vertebral body in rats. J Pain. 2007;8:483–8.
15. Wakai K, Ohtori S, Yamashita M, Yamauchi K, Inoue G, Suzuki M, Orita S, Eguchi Y, Ochiai N, Kishida S, Takaso M, Fukui Y, Hayashi Y, Aoki Y, Kuniyoshi K, Nakamura J, Ishikawa T, Arai G, Miyagi M, Kamoda H, Takahashi K. Primary sensory neurons with dichotomizing axons projecting to the facet joint and the low back muscle in rats. J Orthop Sci. 2010;15:402–6.
16. McLachlan EM, Jänig W, Devor M, Michaelis M. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. Nature. 1993;363:543–6.
17. McLachlan EM, Hu P. Inflammation in dorsal root ganglia after peripheral nerve injury: effects of the sympathetic innervation. Auton Neurosci. 2014;182:108–17.
18. Iwase T, Takebayashi T, Tanimoto K, Terashima Y, Miyakawa T, Kobayashi T, Tohse N, Yamashita T. Sympathectomy attenuates excitability of dorsal root ganglion neurons and pain behaviour in a lumbar radiculopathy model. Bone Joint Res. 2012;1:198–204.
19. Nilsson E, Brisby H, Rask K, Hammar I. Mechanical compression and nucleus pulposus application on dorsal root Ganglia differentially modify evoked neuronal activity in the thalamus. Biores Open Access. 2013;2:192–8.

20. Kobayashi Y, Kurata J, Sekiguchi M, Kokubun M, Akaishizawa T, Chiba Y, Konno S, Kikuchi S. Augmented cerebral activation by lumbar mechanical stimulus in chronic low back pain patients: an FMRI study. Spine (Phila Pa 1976). 2009;34:2431–6.
21. Ng SK, Urquhart DM, Fitzgerald PB, Cicuttini FM, Hussain SM, Fitzgibbon BM. The relationship between structural and functional brain changes and altered emotion and cognition in chronic low back pain brain changes: a systematic review of MRI and fMRI studies. Clin J Pain. 2018;34(3):237–61. https://doi.org/10.1097/AJP.0000000000000534.
22. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci. 2011;31(20):7540–50. https://doi.org/10.1523/JNEUROSCI.5280-10.2011.
23. Staiger TO, Gaster B, Sullivan MD, Deyo RA. Systematic review of antidepressants in the treatment of chronic low back pain. Spine. 2003;28:2540–5.
24. Van Tulder MW, Scholten RJ, Koes BW, Deyo RA. Nonsteroidal anti-inflammatory drugs for low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group. Spine. 2000;25:2501–13.
25. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med. 2005;352:1081–91.
26. Ostelo R, Tulder M, Vlaeyen J, Linton S, Morley S, Assendelft W. Behavioral treatment for chronic low-back pain. Cochrane Database Syst Rev. 2005;1:CD002014.
27. Solomon SD, McMurray JJV, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M. Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005;352:1071–80.
28. Van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM. Cochrane Back Review Group. Muscle relaxants for non-specific low back pain: a systematic review within the framework of the Cochrane collaboration. Spine (Phila Pa 1976). 2003;28:1978–92.
29. Coats TL, Borenstein DG, Nangia NK, Brown MT. Effects of valdecoxib in the treatment of chronic low back pain: results of a randomized, placebo-controlled trial. Clin Ther. 2004;26:1249–60.
30. Vorsanger GJ, Xiang J, Gana TJ, Pascual ML, Fleming RR. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. J Opioid Manag. 2008;4:87–97.
31. Gimbel J, Linn R, Hale M, Nicholson B. Lidocaine patch treatment in patients with low back pain: results of an open-label, nonrandomized pilot study. Am J Ther. 2005;12:311–9.
32. Santana JA, Klass S, Felix ER. The efficacy, effectiveness and safety of 5% transdermal lidocaine patch for chronic low back pain: a narrative review. PM R. 2020;12(12):1260–7. https://doi.org/10.1002/pmrj.12366.
33. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low back pain: an update of the Cochrane review. Spine. 2014.
34. Uhl RL, Roberts TT, Papaliodis DN, Mulligan MT, Dubin AH. Management of chronic musculoskeletal pain. J Am Acad Orthop Surg. 2014;22:101–10.
35. Calvo-Muñoz I, Gómez-Conesa A, Sánchez-Meca J. Physical therapy treatments for low back pain in children and adolescents: a meta-analysis. BMC Musculoskeletal Disord. 2013;14:55.
36. Davidson SRE, Kamper SJ, Haskins R, Robson E, Gleadhill C, da Silva PV, Williams A, Yu Z, Williams CM. Exercise interventions for low back pain are poorly reported: a systematic review. J Clin Epidemiol. 2021;3:S0895-4356(21)00172-4. https://doi.org/10.1016/j.jclinepi.2021.05.020.
37. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain: an update of a Cochrane review. Spine. 2011;36:E825–46.
38. Cramer H, Lauche R, Haller H, Dobos G. A systematic review and meta-analysis of yoga for low back pain. Clin J Pain. 2013;29:450–60.

39. Smith SL, Langen WH. A systematic review of mindfulness practices for improving outcomes in chronic low back pain. Int J Yoga. 2020;13(3):177–82. https://doi.org/10.4103/ijoy.IJOY_4_20.
40. Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2010;74(2):173–6. https://doi.org/10.1212/WNL.0b013e3181c918fc.
41. Rubinstein SM, van Middelkoop M, Kuijpers T, Ostelo R, Verhagen AP, de Boer MR, Koes BW, van Tulder MW. A systematic review on the effectiveness of complementary and alternative medicine for chronic non-specific low-back pain. Eur Spine J. 2010;19:1213–28.
42. Seco J, Kovacs FM, Urrutia G. The efficacy, safety, effectiveness, and cost-effectiveness of ultrasound and shock wave therapies for low back pain: a systematic review. Spine J. 2011;11:966–77.
43. Haile G, Hailemariam TT, Haile TG. Effectiveness of ultrasound therapy on the management of chronic non-specific low back pain: a systematic review. J Pain Res. 2021;14:1251–7. https://doi.org/10.2147/JPR.S277574.
44. Knotkova H, Hamani C, Sivanesan E, Le Beuffe MFE, Moon JY, Cohen SP, Huntoon MA. Neuromodulation for chronic pain. Lancet. 2021;397(10289):2111–24. https://doi.org/10.1016/S0140-6736(21)00794-7.
45. Parr AT, Manchikanti L, Hameed H, Conn A, Manchikanti KN, Benyamin RM, Diwan S, Singh V, Abdi S. Caudal epidural injections in the management of chronic low back pain: a systematic appraisal of the literature. Pain Physician. 2012;15(3):E159–98.
46. Krez A, Liu Y, Kanbour S, Clare S, Waldman S, Stein EM. The skeletal consequences of epidural steroid injections: a literature review. Osteoporos Int. 2021. https://doi.org/10.1007/s00198-021-05986-4.
47. Spoor AB, Öner FC. Minimally invasive spine surgery in chronic low back pain patients. J Neurosurg Sci. 2013;57:203–18.
48. Van Tulder MW, Ostelo R, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft WJ. Behavioral treatment for chronic low back pain: a systematic review within the framework of the Cochrane Back Review Group. Spine. 2001;26:270–81.
49. Xantus G, Zavori L, Matheson C, Gyarmathy VA, Fazekas LM, Kanizsai P. Cannabidiol in low back pain: scientific rationale for clinical trials in low back pain. Expert Rev Clin Pharmacol. 2021;14(6):671–5. https://doi.org/10.1080/17512433.2021.1917379.
50. 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.
51. De Andrés J, Adsuara VM, Palmisani S, Villanueva V, López-Alarcón MD. A double-blind, controlled, randomized trial to evaluate the efficacy of botulinum toxin for the treatment of lumbar myofascial pain in humans. Reg Anesth Pain Med. 2010;35:255–60.
52. Machado D, Kumar A, Jabbari B. Abobotulinum toxin A in the treatment of chronic low back pain. Toxins (Basel). 2016;8(12):374. https://doi.org/10.3390/toxins8120374.
53. Cogné M, Petit H, Creuzé A, Liguoro D, de Seze M. Are paraspinous intramuscular injections of botulinum toxin a (BoNT-A) efficient in the treatment of chronic low-back pain? A randomised, double-blinded crossover trial. BMC Musculoskelet Disord. 2017;18(1):454. https://doi.org/10.1186/s12891-017-1816-6.
54. Jazayeri SM, Ashraf A, Fini HM, Karimian H, Nasab MV. Efficacy of botulinum toxin type a for treating chronic low back pain. Anesth Pain Med. 2011;1(2):77–80. https://doi.org/10.5812/kowsar.22287523.1845.
55. Jabbari B, Ney J, Sichani A, Monacci W, Foster L, Difazio M. Treatment of refractory, chronic low back pain with botulinum neurotoxin A: an open-label, pilot study. Pain Med. 2006;7:260–4.
56. Nathan ST, Roberts CS, Deliberato D. Lumbar paraspinal compartment syndrome. Int Orthop. 2012;36(6):1221–7. https://doi.org/10.1007/s00264-011-1386-4.

57. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155:674–84.
58. Harrington JF, Messier AA, Bereiter D, Barnes B, Epstein MH. Herniated lumbar disc material as a source of free glutamate available to affect pain signals through the dorsal root ganglion. Spine (Phila Pa 1976). 2000;25:929–36.
59. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107:125–33.
60. da Silva LB, Kulas D, Karshenas A, Cairns BE, Bach FW, Arendt-Nielsen L, Gazerani P. Time course analysis of the effects of botulinum neurotoxin type a on pain and vasomotor responses evoked by glutamate injection into human temporalis muscles. Toxins (Basel). 2014;6:592–607.
61. Rand MJ, Whaler BC. Impairment of sympathetic transmission by botulinum toxin. Nature. 1965;206:588–91.
62. Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E. Botulinum A toxin effects on rat jaw muscle spindles. Acta Otolaryngol. 1993;113:400–4.
63. Roberts WJ. A hypothesis on the physiological basis for causalgia and related pains. Pain. 1986;24(3):297–311. https://doi.org/10.1016/0304-3959(86)90116-8.
64. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. Reg Anesth Pain Med. 2016;41(5):621–7. https://doi.org/10.1097/AAP.0000000000000451.
65. Anshus AJ, Oswald J. Erector spinae plane block: a new option for managing acute axial low back pain in the emergency department. Pain Manag. 2021. https://doi.org/10.2217/pmt-2021-0004.
66. Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology- Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70:1707–14.

Chapter 7
Botulinum Toxin Treatment of Plantar Fasciitis (Plantar Fasciopathy)

Introduction

Plantar fasciitis (PF), also referred to as plantar fasciopathy, is a major cause of heel pain in runners and individuals whose job requires heavy footwork. Although, for years, inflammation of the plantar fascia was thought to be the main culprit, many investigators currently favor microtears in the plantar fascia resulting from repeated trauma and degeneration as the main cause of PF [1]. In the United States, approximately two million people are treated for PF annually [2]. In 2007, the annual financial burden from PF to the US economy was estimated as 192 to 376 million dollars [3]. It is believed that 10% of runners demonstrate symptoms of PF during their lifetime [4].

During the acute phase, conventional treatments are often effective. Many patients improve spontaneously after months of discomfort. In approximately 10% of the patients, PF may progress into a chronic form with refractory pain, challenging physicians [5].

The clinical spectrum and treatment options for PF have been presented in detail in recent reviews of the subject [1, 6, 7]. Pain in PF usually affects the medial side of the heel at the insertion area of plantar fascia (Fig. 7.1).

Some patients may experience pain at the middle of the foot (middle of the central band of the fascia), while in others, the pain may spread to the entire foot including the toes. The pain is most noticeable during the initial steps of walking or running. It is usually enhanced by long periods of inactivity preceding activity; weight-bearing also worsens the pain. In the chronic form (symptoms lasting beyond 6 months), calcaneal pain may be experienced at rest and prevent sleep. One-third of the patients complain of bilateral pain.

On examination, the foot looks normal and no weakness is detectable, but approximately 80% of the patients experience associated tightness of the Achilles tendon [8]. In some patients, the skin over the medial calcaneal tuberosity is tender

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_7

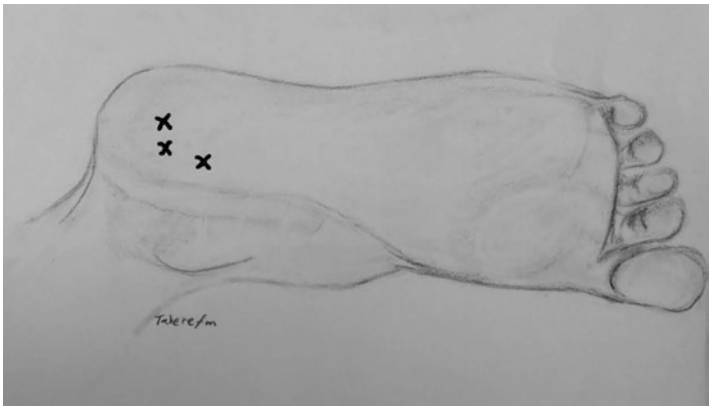

Fig. 7.1 Location of maximum pain in plantar fasciitis. (Drawing courtesy of Tahere Mousavi, MD)

and this tenderness is exaggerated on dorsiflexion of the toes or when standing on tiptoe [9].

Anatomy of Plantar Fascia

Stecco et al. [10] studied the anatomy of the foot in 11 cadavers (mean age 72; 6 males and 5 females) focusing on the plantar fascia and its relationship to the Achilles tendon and adjacent muscles. Serial transverse sections were obtained every 2 cm from the cutis to the interosseous muscles in order to microscopically examine the relationships between the PF, skin, and muscles. Beneath the skin and the underlying fat pad of the foot, PF appears as a glistening, pearl-colored structure extending from the calcaneus to the metatarsopharyngeal (MP) joints. The length of PF is approximately 12 cm from the medial tuberculum to the MP joint. The thickness of PF diminishes significantly as it extends toward the MP joints. At 2 cm from the insertion of the calcaneus, PF is 3.15 mm thick at its center and 1.56 mm laterally. At 10 cm from the insertion point, PF's thickness is 1.41 mm at its center and 0.66 mm laterally.

Most PF fibers are arranged longitudinally, but some fibers are oblique and a few are transverse; the fibers close to the proximal and distal insertions may have transverse arrangement. PF is arranged into three longitudinal fiber groups: medial, central, and lateral (Fig. 7.2a, b).

At the heel, PF fibers are attached to the medial part of the calcaneum (medial tuberculum), cover the heel as a thin layer, and continue into the Achilles tendon. Beneath PF are the deep fascia of the foot which embed three major foot muscles, the flexor halluces, the flexor digitorum brevis, and the flexor digiti minimi. Septae from PF penetrate the deep fascia and connect at different points with all three muscles.

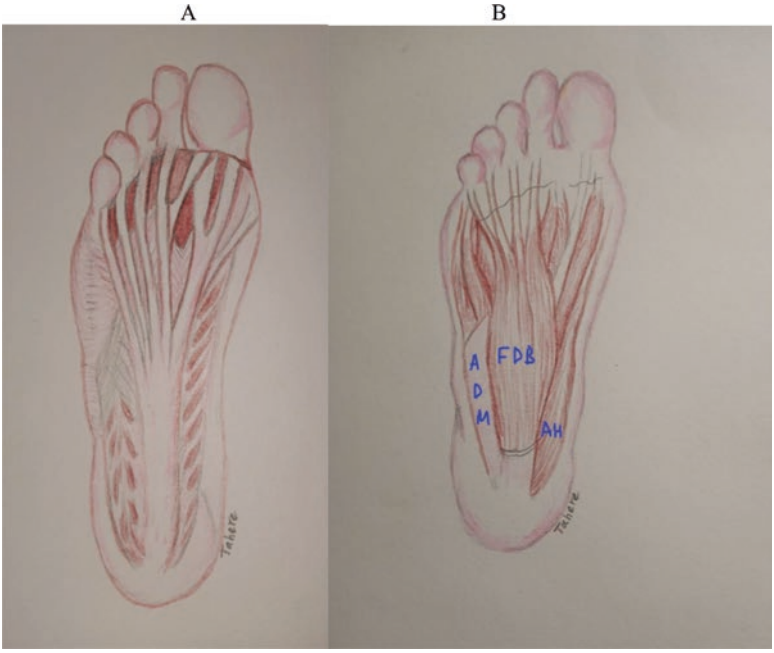

Fig. 7.2 (**a**) Plantar fascia; (**b**) Muscles under the fascia. FDB: flexor digitorum brevis, AH: adductor hallucis, ADM: abductor digiti minimi. (Drawing, courtesy Tahere Mousavi, MD)

Close to the metacarpophalangeal joints, PF divides into five segments each attaching to a metacarpophalangeal joint. The fibers of PF are rich in collagen type1, but also contain hyaluronan which helps PF fibers to easily glide and work like a shock absorber. Plantar fascia is innervated by the terminal branches of the tibial nerve, medial calcaneal, medial and lateral tibial nerves. Plantar fascia is well innervated specially in its medial and lateral parts; it contains an abundance of Pacinian and Ruffinian corpuscles suggesting a role for it in the sole's proprioception [10].

Pathophysiology of Plantar Fasciitis

The plantar fascia serves both static and a dynamic purpose. The static function deals with weight-bearing; it supports the arch of the foot. The fascia contracts and elongates during walking allowing the medial arch to flatten and elevate—the so-called wind glass phenomenon (dynamic phase).

Despite the fact that PF is a clinically well recognized, the details of its pathophysiology remain elusive. Most recent data indicate that pathological changes are more in the form of degeneration (fasciopathy) rather than inflammation (fasciitis) of the fascia, although some elements of the latter are also present. Repetitive trauma to the fascia invariably is a major contributing factor to PF; PF is more

common among overweight individuals. Heel spurs are also common in association with plantar fasciitis suggesting a relation to PF's pathophysiology.

The role of triceps surae muscles in the pathophysiology of PF is increasingly recognized. Contraction of plantar flexor muscles and loss of flexibility of these muscles have been proposed as risk factors for the development of plantar fasciitis [11, 12]. Radiologically, a plantar fascia of thickness of 4 mm or more correlates with clinically active PF. In the study of Stecco et al. [10], 5 of 27 patients with Achilles tendonitis had a plantar fascia thickness of 4.5 mm or more versus none of those in whom radiological data did not support the presence of Achilles tendonitis and PF.

Treatment of Plantar Fasciitis

Treatment of plantar fasciitis consists of nonpharmacological and pharmacological approaches. Surgical intervention is reserved for recalcitrant PF.

In this section, the information on treatment of plantar fasciopathy/fasciitis, for the most part, is derived from Berbyer and Fredericson's recent review [6]. The authors have described treatment approaches in acute (less than 3 months duration), subacute (3–6 months of duration), and chronic >6 months duration) phases of plantar fasciitis. Following the presentation of conventional treatment of plantar fasciitis, a review of the literature on BoNT treatment of plantar fasciitis will be provided using the level of evidence and efficacy (A, B, C, and U) according to the guidelines of the American Academy of Neurology (Appendices 3-1 and 3-2).

Acute Phase: The recommended treatment in this stage consists of stretching exercises, foot orthosis, soft-tissue trigger point manual therapy, calcaneal taping, iontophoresis, and treatment with nonsteroidal, anti-inflammatory agents (NSAID).

Stretching Exercises: Three randomized trials are available with different types of stretching exercises employed in the studies: Achilles stretching and stretching of plantar fascia that can be performed with either weight-bearing or nonweight-bearing and intermittent versus sustained. Stretching is usually performed several times daily and provides 2 to 4 months of relief in the acute phase. The review concluded that stretching is effective in reducing pain and improving function in the acute phase. In a recent double-blind, comparator study [13], plantar stretching was found superior to hot water fomentation, silicon heel pad, and calf stretching in the management of acute plantar fasciitis.

Foot Orthosis: Foot orthosis is commonly used in patients with PF. Both over-the-counter and customized orthotics can be used. In a multicenter study of 236 patients, foot orthosis (prefabricated) plus stretching was found to be superior to stretching alone ($P = 0.022$) [14]. Foot orthosis can be used in all stages of PF.

Soft Tissue Trigger Point Manual Therapy: Retrospective studies suggest temporary reduction of pain in the acute phase using soft tissue trigger point manual therapy.

Iontophoresis: Two double-blind, placebo-controlled studies are available. In the first study of 40 feet from 31 patients, dexamethasone iontophoresis was found superior to placebo and relieved pain for 2 weeks; no long-term benefits were noted, however [15]. In the second study [16], 43 ft from 31 subjects were studied in three groups: (1) iontophoresis with 0.5% acetic acid, (2) with 4% dexamethasone, and (3) with placebo. The investigators found acetic acid to be more effective than steroid iontophoresis and relieved pain for a duration of 2 to 4 weeks.

Calcaneal Taping: This approach was shown to be effective in reducing pain in two prospective blinded studies [17, 18]. This is, however, a very short-term remedy due to skin breakdown that develops after prolonged taping.

Nonsteroidal Anti-inflammatory Drugs (NSAID): Only one double-blind, placebo-controlled study is available pertaining to the use of NSAIDs in PF. Donely et al. [19] studied 29 patients with PF. All patients were using a heel cord stretcher and night splints. NSAID was added to their ongoing treatment. Adding NSAID to the treatment regimen improved the patients' pain modestly.

Subacute Stage: Steroid therapy and acupuncture are both considered options for this stage. Placebo-controlled studies are scarce, however.

Steroid Therapy: Mc Millan et al. [20] showed the efficacy of ultrasound-guided dexamethasone over placebo at 4 weeks after treatment ($P = 0.03$). Several open studies also showed a short-term pain relief from prednisone in PF. A major issue with steroid therapy is rupture of the plantar fascia that occurs in 10% of the patients following injection.

Acupuncture: Zhang et al. [21] studied two groups of subjects (28 in each) blindly with two different techniques of acupuncture (one used as control). One group received acupuncture in acupoint pc7, a location known to affect heel pain. For the second group, acupoint Hegu that has some pain properties was used. The primary outcome was perception of significantly lower heel pain at 1 month post acupuncture. A second study [22] compared acupuncture with NSAID treatment and primary outcomes were measured at 1 and 2 months. Neither study met their primary end point, but both showed considerably more reduction of pain in the acupuncture group.

Chronic Phase: Treatment options for the chronic phase include night splint, extracorporeal shock wave treatment, intracorporeal shock wave treatment, cryosurgery, percutaneous needle fasciotomy, plasma-rich platelet, and botulinum toxin therapy.

Night Splint: Night splint may be helpful in patients who suffer most of their heel pains in the morning. EZ step night splint in combination with NSAID helped 85% of the patients in one study of PF [23].

Shock Wave Treatment: A recent meta-analysis of 11 extracorporeal shock wave treatment studies (ESWT) in plantar fasciitis (four randomized and controlled) showed that this technique can alleviate pain and improve foot function in patients affected by PF [24]. One of the four controlled studies showed significant pain reduction at 12 months post treatment. High-energy ESWT requires nerve block since it is very painful. Intracorporeal shock wave treatment (ISWT)

is a more recent methodology where shock waves are applied directly to calcaneal spur under fluoroscopy. Dogremati et al. [25] assessed the efficacy of ESCT in 50 patients with PF in a blinded, placebo-controlled study. Excellent and good results were significantly higher in the ISWT group compared to the placebo group (92% vs. 24% $P = 0.02$). Complications with ISWT consisted of hematoma, infection, and fascial rupture.

Platelet-Rich Plasma (PRP): This therapeutic approach aims to reduce degeneration and promote healing by local introduction of platelet-rich plasma, which contains an abundance of cytokines. A meta-analysis of 13 clinical trials demonstrated that PRP therapy was superior to placebo, but provided comparable efficacy to corticosteroid injections in plantar fasciitis [26]. However, in a recently reported double-blind study comparing the effect of PRP with corticosteroid injections, PRP therapy was more effective than steroid injections in relieving pain of 114 patients who were followed for a period of 1 year [27]. In a randomized study, Haddad et al. [28] compared the results of PRP therapy with extracorporeal shock wave (ECSW) therapy in 104 patients with chronic plantar fasciitis. Patients' pain was measured by VAS at 2, 4, 6, 12, 16, and 24 months. Both modes of treatment reduced pain, but PRP demonstrated better analgesic effect.

Cryosurgery: This is a minimally invasive, percutaneous, technique which uses the tip of a cryoscope to freeze and destroy intracellular elements of the nerve in PF without destroying epineurium and soft tissue or forming neuromas. No blinded studies are available. One prospective study of 59 patients [29] demonstrated significant improvement in heel pain ($P < 0.0001$) in 90% of the patients, at 1 year postprocedure. The major side effect was the appearance of pain in other foot regions which resolved in 3 to 4 weeks. However, in a recent study that compared the results of cryosurgery with endoscopic plantar fascia release surgery in chronic PF, the latter produced better results over 1 year of follow-up [30].

Dry Needling: In 2014, dry needling was introduced as an alternative treatment to the more aggressive treatments of patients with plantar fasciitis [31]. In this participant blinded (single-blinded) controlled study, dry needling was compared with sham dry needling in 84 patients who had PF for a duration of more than 1 month. At 6 weeks, dry needling provided significant reduction of heel pain (measured by VAS) compared with sham dry needling. A recent meta-analysis of six clinical trials found moderate to low evidence that trigger point (TrP) dry needling improves heel pain intensity and pain-related disability in patients with plantar heel pain [32]. In another study, a combination of dry needling and ESWT was found to be more effective in alleviating pain in PF than either approach alone [33].

Prolotherapy with Dextrose Injection: In a double-blind, placebo-controlled study, Basak and coworkers evaluated the effect of local dextrose injection on pain of patients with plantar fasciitis [34]. Sixty-nine patients were randomized into two groups. Group one received 5 cc of 30% dextrose in 4 cc of saline (0.9% NaCl) and 1 cc of 2% lidocaine combined, whereas group two (control) received 9 cc of saline and 1 cc of 2% lidocaine combined. Five injection sites were chosen: 1

and 2, where plantar fascia attaches to the first and fifth metatarsal points, and 3, 4, and 5, where plantar fascia attaches to the heel (medial, lateral, and midpoint of the plantar fascia). Injections were performed twice at three-week intervals. Improvements were measured at seventh and 15th weeks after initiation of injections using visual analog scale (VAS), foot function index, and reduction in plantar fascia thickness and were found to be significantly higher in the dextrose injected group compared to the control group ($P < 0.001$). Injection of dextrose is believed to lead to increase in growth factors (platelet and connective tissue derived and epithelial) and accumulation of cytokines local tissue promoting tissue regeneration.

In conclusion, treatment of chronic plantar fasciitis is difficult. Treatment with steroid injections, extracorporeal shock wave, and dry needling is only partially effective and the results are often short-lived. Side effects associated with such approaches include plantar fascia rupture (with steroid injections) and pain of the procedure itself (with extracorporeal shock wave therapy), leaving the door open for novel treatment with easier and safer therapeutic approaches.

BoNT Treatment of Plantar Fasciitis

Four blinded, placebo-controlled studies have been published on this subject (Table 7.1) [35–38]. The first placebo-controlled, blinded investigation on the efficacy of BoNTs in plantar fasciitis was conducted by the author's group at the Walter Reed Army Medical Center (WRAMC) in 2005 [35]. In this study, the efficacy of onabotulinumtoxinA was investigated in 27 patients (a total of 43 ft) with chronic plantar fasciitis. All patients had chronic PF with the duration of their symptoms exceeding 6 months. The subjects were recruited from the Departments of Neurology and Physical Medicine at WRAMC. Those with pending litigation, secondary gain and those who were on narcotic agents were excluded from the study. OnabotulinumtoxinA was used for the study at a dilution of 100 units/cc. The toxin was introduced into the foot using a ¾ inch needle at two points. The first point, the tender area in the medial aspect of the heel near the calcaneal tuberosity, received 40 units. The second point, between posterior line of the heel and middle of the foot, received 30 units. The total dose of onaA per foot was 70 units (Fig. 7.3). Controls received the same volume of normal saline solution at the same sites. Patients with bilateral symptoms received an injection of onabotulinumtoxinA in one foot and an injection of saline solution in the contralateral foot. Patients pain response and improvement of foot function was measured by Visual Analog Scale (VAS), Maryland Foot Score (MFS) and Pressure Algometry response at 3 and at 8 weeks after injection. The primary outcome was improvement of the visual analog scale for pain. The study revealed statistically significant changes in the treatment group. Compared with placebo injections, the botulinum toxin A group improved in all measures: Visual Analog Scale ($P < 0.005$), Maryland Foot Score ($P = 0.001$), and

Table 7.1 Blinded and placebo-controlled studies assessing the efficacy of botulinum neurotoxins in plantar fasciitis

Authors and year	Type of study	# Pts	Type of toxin	Dose/units; mode of injection	Measures	Outcome	Results
Babcock et al. (2005) [35]	DB, PC, PD, class II	34	onaA	70 u, two injections[a]	Vas, MFS, PA	VAS at 3 weeks and 8 weeks	All three measures improved
				40 u and 30 u			VAS: $P = 0.005$
							MFS: $P = 0.001$
							PA: $P = 0.003$
Huang et al. (2010) [36]	DB, PC, PD, class II	50	onaA	50 u, single injection into PF, posterior approach below calcaneum	VAS and PF thickness on sonography	VAS and Plantar fascia thickness at 3 weeks and 3 months	VAS improved and plantar fascia thickness was reduced ($P < 0.001$)
Ahmed et al. (2017) [37]	DB, PC, PD, class II	50	incoA	100 u, Single injection into plantar fascia where it was most tender at medial calcaneus	Vas, FAAM	VAS and FAAM at 6 months and 12 months	VAS and FAAM improved significantly at 6 and 12 months ($P < 0.01$)
Abbasian et al. (2020) [38]	SB, PC, PD, class III	32	BoNT-A	70 u, single injection into the Proximal third of medial head of GC	VAS, AOFAS	VAS and AOFAS score at 1, 3, 6, and 12 months	Mean VAS reduced at 1, 3, 6, and 12 months ($P < 0.001$). AOFAS score increased in toxin group at 1, 3, 6, and 12 months ($P < 0.01$).
							Patient satisfaction increased at 12 months

DB double-blind, *PC* placebo-controlled, *PD* Parallel design, *onaA* onabotulinumtoxinA (Botox), *VAS* Visual Analog Scale, *MFS* Maryland Foot Score, *PA* pressure algometry, *GC* Gastrocnemius, *AOFAS* American Orthopaedic Foot & Ankle Society, *FAAM* Foot and Ankle Ability Measure

[a]Sites of injection: 40 units into the tender area at the medial aspect of the heel near calcaneal tuberosity and 30 u into the plantar fascia, between the anterior border of calcaneus and middle of the foot

the pressure algometry response ($P = 0.003$). No serious side effects were noted by either the patients or the physicians.

In the same year, Placzek et al. [39] reported on the effects of a single injection of botulinum toxin A in an open label study of 9 patients. All patients had PF and had failed at least two of the following four treatments: physical therapy, custom/

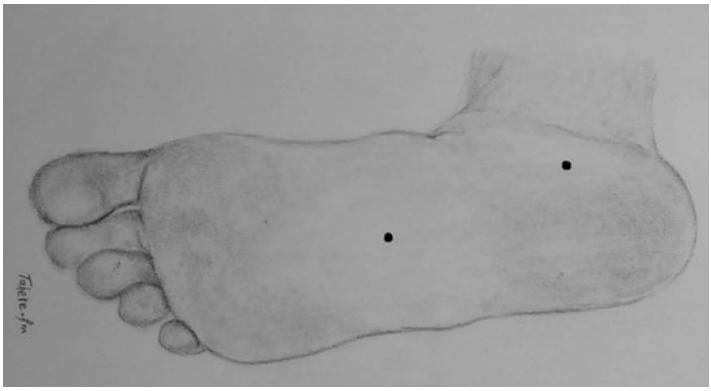

Fig. 7.3 Site of injections recommended by Babcock et al. [35] for BoNT treatment of PF. (Drawing, courtesy of Tahere Mousavi, MD)

prefabricated orthotics, acupuncture, and extracorporeal shock therapy. A total dose of 200 units of aboA was injected subfascially in four directions through one puncture introduced at the origin of the plantar fascia. The authors reported that this single injection significantly reduced VAS pain scores from 2 weeks after injection to week 52 (week 2 to 39: $P = 0.01$; week 52: $P = 0.04$).

Huang et al. [36] conducted the second randomized, double-blind study on 50 patients with chronic unilateral plantar fasciitis. Patients received either 50 units of onabotulinumtoxinA or a comparable volume of saline under ultrasonographic guidance. Outcome measures were changes in VAS (pain), gait assessment (the maximal center of pressure velocity during the first-step loading response), as well as measured changes in the thickness of the plantar fascia and the fat pad. These assessments were made at baseline, 3 weeks and 3 months after the injection.

At 3 weeks and 3 months, both VAS score and plantar fascial thickness (measured by sonography) decreased significantly ($P < 0.001$) in the symptomatic foot. Injection of OnaA caused no footpad atrophy. No side effects were noted. The authors concluded that botulinum toxin A was safe and effective for treatment of chronic plantar fasciitis, but recognized a need for long-term studies.

In another randomized, blinded study, Ahmed et al. [37] assessed the efficacy of a single injection of 50 units of incobotulinumtoxinA in 50 patients with plantar fasciitis. The injection was performed into plantar fascia where it was most tender at medial calcaneus. They reported significant improvement ($P < 0.01$) of VAS and Foot and Ankle Ability Measure (FAAM) at 6 months and at 12 months after the toxin injection.

Recently, a single-blind study reported on the injection of BoNT-A into the proximal third of medial head of the gastrocnemius muscle in 32 patients with plantar fasciitis [38]. The toxin was introduced by a single injection (70 units) into this area. The effect on pain was evaluated by VAS and by the American Orthopedic Foot and

Ankle Society score (AOFAS). The rational for injecting into proximal gastrocnemius muscle was previous reports that in PF, triceps surae (soleus and gastrocnemius) demonstrate significantly increased tone [40] and, that surgical resection of proximal medical head of gastrocnemius muscle can relive pain of PF [41]. At 12-month follow-up, the mean VAS in the placebo group decreased from 7.8 to 4 and from 8 to 0.33 in the BoNT-A group. Furthermore, the mean AOFAS scores increased from 48.4 to 65.3 in the placebo group and from 45.5 to 90.6 in the BoNT-A group. The postinjection scores in the BoNT-A group were significantly higher than those in the placebo group ($P < 0.001$).

Case Report

A 73-year-old gentleman, an avid tennis player, noted discomfort at the bottom of his feet approximately 8 years ago. The discomfort was particularly noticeable after playing a few games of tennis; over months, the discomfort gradually developed into pain. The pain localized to the heels and around the medial part of both feet, often interrupting his game of tennis.

Over the years, the patient tried a variety of pharmacological and nonpharmacological measures for management of his heel pain. Stretching, orthosis, and night splints offered little help. Nonsteroidal anti-inflammatory drugs had minimal effect. A couple of sessions of acupuncture "helped some," but the effect lasted only a few days. Treatment with steroids did not help. Following an internet search and coming across BoNT literature for plantar fasciitis, the patient decided to visit the Yale Botulinum Toxin Clinic for an evaluation.

The neurological examination including cognition, cranial nerves, sensory, motor and cerebellar functions, speech, and gait was normal. He rated his pain during "bad days" as 8 out of 10 on VAS. He pointed to the regions of pain in his feet that mainly involved the heels, but also extended to the center of the feet bilaterally. Following an assessment of pain distribution, onabotulinumtoxinA was injected into both feet using the methodology of Babcock et al. [36]. A total of 70 units was injected (40 and 30 units at two points, Fig. 7.3). Within days, the patient reported significant improvement of his heel pain; the pain relief lasted for 7 months. The second treatment with the same dose also produced pain relief for 7 to 8 months. For the third treatment, since emerging literature had suggested that tense triceps surae shows increased tone and may possibly contribute to the magnitude of pain in PF, an additional 30 units were injected into the soleus muscle. The patient came for his fourth treatment 9 months later and reported a longer period of relief and was very satisfied with the onaA treatment. He reported no side effects.

Comparator Studies

Three blinded studies have compared the effect of BoNT injection with steroid injection in patients with plantar fasciitis [42–44]. Díaz-Llopis et al. [42], in a single-blind study, compared the effect of BoNT and a mixture of corticosteroid with a local anesthetic agent in 28 patients. All patients had chronic plantar fasciitis. In the botulinum toxin group, the authors injected onabotulinumtoxinA into the plantar fascia using the same methodology and dose as described above by Bobcock and her coworkers [36]. In the other group, the patients were injected with betamethasone plus 0.5 ml of 1% mepivacaine. A number of different measures were used to evaluate the changes in pain and function in response to the two therapeutic approaches. At 1 month, both treatments improved all measures significantly, but onaA relieved pain more than betamethasone ($P = 0.06$). Improvement of different measures with onaA vs. betamethasone were recorded and showed significant improvement in the onaA group; the measures assessed included pain ($P = 0.001$), function ($P < 0.001$), footwear ($P = 0.004$), and self-perceived foot health ($P < 0.001$). At 6 months, the above values continued to improve further in the onaA group, while most of the improved values faded in the betamethasone group. The authors concluded that onabotulinumtoxinA is more effective in improving heel pain and foot function in patients with plantar fasciitis; the authors noted that improvements after onaA injection lasted longer than that observed with injection of betamethasone. In a subsequent open label study of 24 patients from this study who had shown significant response to BoNT-A at 6 months, the authors demonstrated continued improvement with onabotulinumtoxinA at 12 months [45]. In another study (randomized and double-blind), the effect of abobotulinumtoxinA and plantar stretching was compared with steroid injection and plantar stretching in 36 patients with plantar fasciitis (19 received BoNT-A and 17 received steroid) [43]. Investigators injected 100 units of toxin into the lateral and 100 units into the medial gastrocnemius as well as 50 units into the soleus muscle. The steroid (dexamethasone isonicotinate, 8 mg) was mixed with 2% lidocaine and injected into the medial surface of the foot just superior to the plantar fascia. Patients' level of pain was assessed by VAS and foot function by Maryland Foot and Ankle Score (MFAS) as well as American Orthopaedic Foot and Ankle Score (AOFAS). On 6 successive evaluations, weeks apart, the group that received BoNT-A demonstrated more improvement of VAS, MFAS, and AOFAS scores compared to the group that received dexamethasone and lidocaine (P values varying from 0.02 to 0.0001).

In a subsequent, randomized, double-blind study [44], the same group of investigators, using a different method of injection, compared the effect of various agents: anesthetic ropivacaine compared with abobotulinumtoxinA and betamethasone in three different groups. Clinical outcomes were measured by VAS for pain and by MFAS for pain and function, as well as the measurement of plantar fascia thickness by ultrasound. Patients were evaluated at baseline and at 2, 4, 12, and 24 weeks after injections. Under ultrasound guidance, the test agent was introduced by a single injection at the maximum tenderness point; the needle was placed subfascially near

the insertion of the plantar fascia in a fan-shaped manner. The dose of the three tested agents was as follows: abobotulinumtoxinA, 200 units, ropivacaine, 5 cc (7.5 mg/cc), betamethasone sodium phosphate, and betamethasone acetate equivalent of 3 mg and 2.71 mg of betamethasone, respectively. In regard to all evaluated outcomes, patients of all three groups improved after injections. There was no significant difference between the three groups statistically. The pain relief and functional improvements from the three different treatments were maintained during the 6 months of follow-up. BoNT-A and betamethasone injections reduced the thickness of plantar fascia significantly during the latter weeks of the study, whereas ropivacaine did not.

How Does BoNT Injections Improve Pain in Plantar Fasciitis?

BoNT injections may relieve pain in plantar fasciitis via several mechanisms including their effect on pain fibers, muscles, plantar fascia itself as well as via an anti-inflammatory effect:

- Several animal studies have shown that BoNT-A inhibits the release of major pain mediators such as calcitonin-gene-related peptide, substance P and glutamate from peripheral terminals and/or sensory neurons [46–49]. The type B toxin also inhibits the release of substance P from dorsal root ganglion neurons and the sensory neurons of the spinal cord [50, 51]. Furthermore, there is also evidence that, at least, part of the analgesic effects of BoNT-A is exerted through central mechanisms either through retrograde transfer of the toxin to central neural stations or through other unknown mechanisms [52, 53]. OnabotulinumtoxinA is now approved by FDA and European regulatory committees for treatment of chronic migraine. Also, published controlled studies have provided compelling evidence for the efficacy of BoNTs in several other pain disorders such as trigeminal, postherpetic and posttraumatic neuralgias [54, 55].
- The injected toxin most likely reaches the tense muscles which are located under a thickened and stiff plantar fascia. Relaxation (and reversible atrophy) of these muscles (flexor digitorum brevis and flexor pollicis brevis) via the anticholinergic effects of BoNTs can reduce fascial tension and resultant pain. It is possible that injection close to the medial heel might also influence and relax the distal part of the soleus muscle. As discussed above, it is believed that increased tone of the triceps surae (soleus and gastrocnemius muscles) is often associated with

plantar fasciitis. In one study, authors have shown that injection of BoNT into only the proximal medial gastrocnemius muscle can relieve the pain and discomfort of plantar fasciitis [38].
– Reduced thickness of plantar fascia, observed in double-blind and comparative studies, after injection of BoNT-A can contribute to the analgesic effect of the toxin [44].
– Although current literature downplays inflammation as the cause of plantar fasciitis, chronic pain conditions are often associated with some degrees of local inflammation. Intramuscular injection of botulinum toxin-A has been shown to reduce local inflammatory changes in the tissue based on BoNT-A injection in animal models of local pain [56].

Conclusion

Plantar fasciitis affects a large number of individuals (two million in the United States) and, in its chronic form, is a disabling condition. Current effective treatments for the chronic form of PF such as steroid injections and extracorporeal shock therapy often cause temporary relief, are hard to tolerate and can have undesirable side effects (plantar tearing in case of steroids). Botulinum toxin injections provide an alternative treatment that is easy to employ, well tolerated and in controlled and open label studies of over 300 patients has caused no serious side effects. In the blinded studies cited above (Table 7.1), the efficacy of BoNT injections in PF has been strongly suggested via employment of two different techniques. Using the efficacy criteria of the guidance and development subcommittee of the American Academy of Neurology [51, 52], the efficacy level for the injection into the plantar fascia and medial aspect of the heel [35, 36, 39] qualifies as B (probably effective) based on two class II studies [35, 36]. For the technique of gastrocnemius injection, the level of efficacy is currently C (possibly effective) based on one class II study [37]. The author, who had designed the technique of the original study (B Jabbari) [35], later used a modification of that technique during his 11-year tenure (2004–2015) at Yale University as director of the botulinum toxin treatment program. He noticed better results in several patients with PF when bilateral soleus injections (in the case of onaA, 20 units on each side injected into two sites, each 10 units) (Fig. 7.4) were added to the original protocol that injected the plantar fascia and medial heel only.

It should be noted that, so far, all controlled and blinded studies of botulinum toxin in plantar fasciitis have been conducted in small numbers of patients. Multicenter studies in large cohorts are needed to verify the efficacy of BoNT treatment in improving pain and foot function in chronic plantar fasciitis.

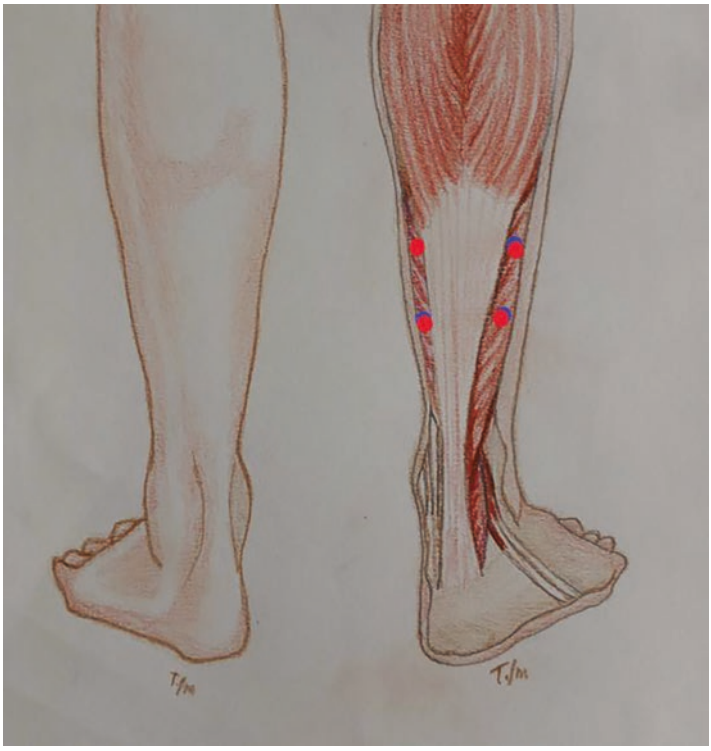

Fig. 7.4 Recommended sites of soleus injections in plantar fasciitis. (Drawing, courtesy of Tahere Mousavi, MD)

References

1. Sullivan J, Pappas E, Burns J. Role of mechanical factors in the clinical presentation of plantar heel pain: implications for management. Foot (Edinb). 2020;42:101636. https://doi.org/10.1016/j.foot.2019.08.007.
2. Riddle DL, Pulisic M, Pidcoe P, Johnson RE. Risk factors for plantar fasciitis: a matched case-control study. J Bone Joint Surg Am. 2003;85(5):872–7. https://doi.org/10.2106/00004623-200305000-00015. Erratum in: J Bone Joint Surg Am. 2003;85-A(7):1338
3. Tong KB, Furia J. Economic burden of plantar fasciitis treatment in the United States. Am J Orthop (Belle Mead NJ). 2010;39(5):227–31.
4. Chandler TJ, Kibler WB. A biomechanical approach to the prevention, treatment and rehabilitation of plantar fasciitis. Sports Med. 1993;15:344–52.
5. Jastifer JR, Catena F, Doty JF, Stevens F, Coughlin MJ. Low-level laser therapy for the treatment of chronic plantar fasciitis: a prospective study. Foot Ankle Int. 2014.
6. Berbrayer D, Fredericson M. Update on evidence-based treatments for plantar fasciopathy. PMR. 2014;6:159–69.
7. Tahririan MA, Motififard M, Tahmasebi MN, Siavashi B. Plantar fasciitis. J Res Med Sci. 2012;17(8):799–804.

8. Singh D, Angel J, Bentley G, Trevino SG. Fortnightly review. Plantar fasciitis. BMJ. 1997;315:172–5.
9. Young CC, Rutherford DS, Neidfeldt MW. Treatment of plantar fasciitis. Am Fam Physician. 2001;63:467–74.
10. Stecco C, Corradin M, Macchi V, Morra A, Porzionato A, Biz C, De Caro R. Plantar fascia anatomy and its relationship with Achilles tendon and paratenon. J Anat. 2013;223:665–76.
11. Cheung JT, Zhang M, An KN. Effect of Achilles tendon loading on plantar fascia tension in the standing foot. Clin Biomech (Bristol, Avon). 2006;21:194–203.
12. Kibler WB, Goldberg C, Chandler TJ. Functional biomechanical deficits in running athletes with plantar fasciitis. Am J Sports Med. 1991;19:66–71.
13. Gupta R, Malhotra A, Masih GD, Khanna T, Kaur H, Gupta P, Kashyap S. Comparing the role of different treatment modalities for plantar fasciitis: a double blind randomized controlled trial. Indian J Orthop. 2020;54(1):31–7. https://doi.org/10.1007/s43465-019-00038-w.
14. Pfeffer G, Bacchetti P, Deland J, Lewis A, Anderson R, Davis W, Alvarez R, Brodsky J, Cooper P, Frey C, Herrick R, Myerson M, Sammarco J, Janecki C, Ross S, Bowman M, Smith R. Comparison of custom and prefabricated orthoses in the initial treatment of proximal plantar fasciitis. Foot Ankle Int. 1999;20:214–21.
15. Gudeman SD, Eisele SA, Heidt RS Jr, Colosimo AJ, Stroupe A. Treatment of plantar fasciitis by iontophoresis of 0.4% dexamethasone. A randomized, double-blind, placebo-controlled study. Am J Sports Med. 1997;25:312–6.
16. Osborne HR, Alison GT. Treatment of plantar fasciitis by Low Dye taping and iontophoresis: short-term results of a double-blinded, randomized, placebo controlled clinical trial of dexamethasone and acetic acid. Br J Sports Med. 2006;40:544–9.
17. Lynch DM, Goforth WP, Martin JE, Odom RD, Preece CK, Kotter MW. Conservative treatment of plantar fasciitis: a prospective study. J Am Podiatr Med Assoc. 1998;88:375–80.
18. Hyland MR, Webber-Gaffney A, Cohen L, Lichtman PT. Randomized controlled trial of calcaneal taping, sham taping, and plantar fascia stretching for the short-term management of plantar heel pain. J Orthop Sports Phys Ther. 2006;36(6):364–71. https://doi.org/10.2519/jospt.2006.2078.
19. Donley BG, Moore T, Sferra J, Gozdanovic J, Smith R. The efficacy of oral nonsteroidal anti-inflammatory medication (NSAID) in the treatment of plantar fasciitis: a randomized, prospective, placebo-controlled study. Foot Ankle Int. 2007;28:20–3.
20. McMillan AM, Landorf KB, Gilheany MF, Bird AR, Morrow AD, Menz HB. Ultrasound guided corticosteroid injection for plantar fasciitis: randomized controlled trial. BMJ. 2012;344:e3260.
21. Zhang SP, Yip TP, Li QS. Acupuncture treatment for plantar fasciitis: a randomized controlled trial with six months follow-up. Evid Based Complement Alternat Med. 2011;2011:154108. https://doi.org/10.1093/ecam/nep186.
22. Karagounis P, Tsironi M, Prionas G, Tsiganos G, Baltopoulos P. Treatment of plantar fasciitis in recreational athletes: two different therapeutic protocols. Foot Ankle Spec. 2011;4:226–34.
23. Al-Bluwi MT, Sadat-Ali M, Al-Habdan IM, Azam MQ. Efficacy of EZStep in the management of plantar fasciitis: a prospective, randomized study. Foot Ankle Spec. 2011;4:218–21.
24. Melese H, Alamer A, Getie K, Nigussie F, Ayhualem S. Extracorporeal shock wave therapy on pain pain and foot functions in subjects with chronic plantar fasciitis: systematic review of randomized controlled trials. Disabil Rehabil. 2021;26:1–8. https://doi.org/10.1080/09638288.2021.1928775.
25. Dogramaci Y, Kalaci A, Emir A, et al. Intracorporeal pneumatic shock application for the treatment of chronic plantar fasciitis: a randomized, double blind prospective clinical trial. Arch Orthop Trauma Surg. 2010;130:541–6.
26. Yu T, Xia J, Li B, Zhou H, Yang Y, Yu G. Outcomes of platelet-rich plasma for plantar fasciopathy: a best-evidence synthesis. J Orthop Surg Res. 2020;15(1):432. https://doi.org/10.1186/s13018-020-01783-7.

27. Peerbooms JC, Lodder P, den Oudsten BL, Doorgeest K, Schuller HM, Gosens T. Positive effect of platelet-rich plasma on pain in plantar fasciitis: a double-blind multicenter randomized controlled trial. Am J Sports Med. 2019;47(13):3238–46. https://doi.org/10.1177/0363546519877181.
28. Haddad S, Yavari P, Mozafari S, Farzinnia S, Mohammadsharifi G. Platelet-rich plasma or extracorporeal shockwave therapy for plantar fasciitis. Int J Burns Trauma. 2021;11(1):1–8.
29. Allen BH, Fallat LM, Schwartz SM. Cryosurgery: an innovative technique for the treatment of plantar fasciitis. J Foot Ankle Surg. 2007;46(2):75–9. https://doi.org/10.1053/j.jfas.2007.01.006.
30. Çatal B, Bilge A, Ulusoy RG. Endoscopic plantar fascia release versus cryosurgery for the treatment of chronic plantar fasciitis: a prospective randomized study. J Am Podiatr Med Assoc. 2020;110(5):Article_3. https://doi.org/10.7547/18-082.
31. Cotchett MP, Munteanu SE, Landorf KB. Effectiveness of trigger point dry needling for plantar heel pain: a randomized controlled trial. Phys Ther. 2014;94(8):1083–94. https://doi.org/10.2522/ptj.20130255.
32. Llurda-Almuzara L, Labata-Lezaun N, Meca-Rivera T, Navarro-Santana MJ, Cleland JA, Fernández-de-Las-Peñas C, Pérez-Bellmunt A. Is dry needling effective for the management of Plantar heel pain or plantar fasciitis? An updated systematic review and meta-analysis. Pain Med. 2021:pnab114. https://doi.org/10.1093/pm/pnab114.
33. Bagcier F, Yilmaz N. The impact of extracorporeal shock wave therapy and dry needling combination on pain and functionality in the patients diagnosed with plantar fasciitis. J Foot Ankle Surg. 2020;59(4):689–93. https://doi.org/10.1053/j.jfas.2019.09.038.
34. Mansiz-Kaplan B, Nacir B, Pervane-Vural S, Duyur-Cakit B, Genc H. Effect of dextrose prolotherapy on pain intensity, disability, and plantar fascia thickness in unilateral plantar fasciitis: a randomized, controlled, double-blind study. Am J Phys Med Rehabil. 2020;99(4):318–24. https://doi.org/10.1097/PHM.0000000000001330.
35. 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.
36. 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.
37. Ahmad J, Ahmad SH, Jones K. Treatment of plantar fasciitis with botulinum toxin. Foot Ankle Int. 2017;38(1):1–7. https://doi.org/10.1177/1071100716666364.
38. Abbasian M, Baghbani S, Barangi S, Fairhurst PG, Ebrahimpour A, Krause F, Hashemi M. Outcomes of ultrasound-guided gastrocnemius injection with botulinum toxin for chronic plantar fasciitis. Foot Ankle Int. 2020;41(1):63–8. https://doi.org/10.1177/1071100719875220.
39. Placzek R, Deuretzbacher G, Buttgereit F, Meiss AL. Treatment of chronic plantar fasciitis with botulinum toxin A: an open case series with a 1 year follow up. Ann Rheum Dis. 2005;64:1659–61.
40. Bolívar YA, Munuera PV, Padillo JP. Relationship between tightness of the posterior muscles of the lower limb and plantar fasciitis. Foot Ankle Int. 2013;34(1):42–8. https://doi.org/10.1177/1071100712459173.
41. Abbassian A, Kohls-Gatzoulis J, Solan MC. Proximal medial gastrocnemius release in the treatment of recalcitrant plantar fasciitis. Foot Ankle Int. 2012;33(1):14–9. https://doi.org/10.3113/FAI.2012.0014.
42. 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.
43. Elizondo-Rodriguez J, Araujo-Lopez Y, Moreno-Gonzalez JA, Cardenas-Estrada E, Mendoza-Lemus O, Acosta-Olivo C. A comparison of botulinum toxin a and intralesional steroids

for the treatment of plantar fasciitis: a randomized, double-blinded study. Foot Ankle Int. 2013;34(1):8–14. https://doi.org/10.1177/1071100712460215.
44. Elizondo-Rodríguez J, Simental-Mendía M, Peña-Martínez V, Vilchez-Cavazos F, Tamez-Mata Y, Acosta-Olivo C. Comparison of botulinum toxin A, corticosteroid, and anesthetic injection for plantar fasciitis. Foot Ankle Int. 2021;42(3):305–13. https://doi.org/10.1177/1071100720961093.
45. Díaz-Llopis IV, Gómez-Gallego D, Mondéjar-Gómez FJ, López-García A, Climent-Barberá JM, Rodríguez-Ruiz CM. Botulinum toxin type A in chronic plantar fasciitis: clinical effects one year after injection. Clin Rehabil. 2013;27(8):681–5. https://doi.org/10.1177/0269215512469217.
46. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;358:137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040.
47. Shao YF, Xie JF, Ren YX, Wang C, Kong XP, Zong XJ, Fan LL, Hou YP. The inhibitory effect of botulinum toxin type A on rat pyloric smooth muscle contractile response to substance P in vitro. Toxins (Basel). 2015;7(10):4143–56. https://doi.org/10.3390/toxins7104143.
48. Durham PL, Cady R, Cady R. Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache. 2004;44(1):35–42.; discussion 42–3. https://doi.org/10.1111/j.1526-4610.2004.04007.x.
49. Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int. 2008;101(3):366–70. https://doi.org/10.1111/j.1464-410X.2007.07312.x.
50. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155(4):674–84. https://doi.org/10.1016/j.pain.2013.12.009.
51. Huang PP, Khan I, Suhail MS, Malkmus S, Yaksh TL. Spinal botulinum neurotoxin B: effects on afferent transmitter release and nociceptive processing. PLoS One. 2011;6(4):e19126. https://doi.org/10.1371/journal.pone.0019126. Erratum in: PLoS One. 2011;6(8). https://doi.org/10.1371/annotation/1fe31fa2-e930-4a72-a208-64eb42d99f02. Erratum in: PLoS One. 2011;6(8). https://doi.org/10.1371/annotation/7b989904-0cf4-4f2d-9626-6bf3ef6646c5.
52. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459.
53. Caleo M, Spinelli M, Colosimo F, Matak I, Rossetto O, Lackovic Z, Restani L. Transynaptic action of botulinum neurotoxin type A at central cholinergic boutons. J Neurosci. 2018;38(48):10329–37. https://doi.org/10.1523/JNEUROSCI.0294-18.2018.
54. Brown EA, Schütz SG, Simpson DM. Botulinum toxin for neuropathic pain and spasticity: an overview. Pain Manag. 2014;4(2):129–51. https://doi.org/10.2217/pmt.13.75.
55. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes -an evidence based review. Toxicon. 2018;147:120–8. https://doi.org/10.1016/j.toxicon.2018.01.017.
56. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107(1–2):125–33. https://doi.org/10.1016/j.pain.2003.10.008.

Chapter 8
Botulinum Toxin Treatment of Myofascial Pain Syndrome and Fibromyalgia

Introduction

Myofascial pain syndrome (MFPS) is a common pain disorder and a major source of work interruption and disability. Up to 85% of people experience myofascial pain sometimes during their lifetime [1]. It is characterized by focal muscle pain felt spontaneously or evoked by pressure against trigger points. Trigger points (TrPs) include tight muscle bands (taut band) with sensitivity to touch, both to induce pain (local or referred) and/or induce muscle twitch response. Trigger points can be active or latent (inactive). Active trigger points induce spontaneous pain as well as pain after being pressed, whereas latent TrPs may generate pain only when they are pressed upon. Latent TrPs can be activated by prolonged exercise, low-load repetitive muscle activity, persistent stress, and prolonged ischemia of the muscle [2].

The criteria set by Simons in 1999 for definition of trigger points [3] is generally accepted and currently used by many in clinical practice (Table 8.1).

These criteria have been studied and have shown good interexaminer reproducibility and reliability [4].

Myofascial pain syndrome is reported with a variable prevalence of 30–93%; it has a peak age at presentation between ages 30 and 50 years. Myofascial pain syndrome is more common among women and in individuals with decreased motor activity [5–7].

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_8

Table 8.1 Simons's criteria for identifying trigger points

1. Presence of a palpable taut band in a skeletal muscle
2. Presence of hypersensitive tender spots in the taut bands
3. Local twitch response provoked by snapping of the taut bands
4. Reproduction of the typical referred pain pattern of trigger point in response to compression

Anatomy and Pathophysiology of Myofascial Pain Syndrome (MFPS)

The muscles of patients with MPS demonstrate trigger points. The trigger points, often multiple, consist of hypersensitive indurated muscle fibers called "taut bands." Taut bands show increased number of spontaneous, small amplitude, on-going end-plate potential discharges at rest indicating rich acetylcholine content [8]. Increased level of acetylcholine in these muscle bands makes them sensitive to touch and elicits the "twitch response" [9].

Exactly how trigger points develop in the muscles of patients with MFPS is unclear. The integral theory of Simons [3] proposes ischemic/metabolic derangement of the muscle and local failure of energy. Hypoperfused muscle develops areas of low pH that inhibit acetylcholine esterase and lead to local accumulation of acetylcholine [10].

Development of trigger points in the muscle causes spontaneous or pressure-induced local muscle pain and referred pain. Pain may be partly related to low pH, increased local accumulation of protons (H+), and acid-sensing channels in the extracellular fluid of trigger points affecting terminal nerve endings.

Shah et al. [11, 12] investigated the mechanism of pain induction in MFPS. They have shown increased levels of pain mediators, such as substance P and CGRP, as well as increased inflammatory mediators such as cytokines in both active and latent trigger points (less in latent). Local accumulation of pain mediators and inflammatory elements leads to peripheral sensitization of nerve endings and dorsal root ganglia. Continued peripheral sensitization causes central sensitization of spinal cord neurons leading to pain chronicity [13].

Climent et al. [14] discussed the pathophysiology of trigger points (TrPs) in detail in a recent review. Neuroimaging studies have shown that biomechanical properties and blood flow of active and latent TrPs are quantifiably distinct from those of the healthy tissue [15].

Treatment

The first description of myofascial pain is credited to Guillaume de Baillou in the year 1600 [16]. In 1904, Gowers wrote that accumulation of inflamed connective tissue in the affected muscle is responsible for creating painful muscle nodules.

Almost 70 years ago, Travell and Rinzler [17] coined the term "myofascial trigger points." The Delphi study criteria based on an international consensus for diagnosis of trigger point requires presence of at least two of the three following: taut band, hypersensitive spot, and induction of referred pain when pressure is applied to the taut band [18].

Through the years, a number of pharmacological and nonpharmacological approaches were employed for treatment of myofascial pain syndrome. Unfortunately, majority of the reported studies represent uncontrolled data. Nonpharmacological approaches include the following measures:

- Physical therapy can increase the range of motion and elevate pain threshold, including massage, compression, stretching, applying superficial heat (74.5 °C), [19–21]. Yoga, meditation, behavioral therapy, and acupuncture relax the muscle and raise the pain threshold. Acupuncture has been found to be partially effective in a controlled study [22].
- Superficial heat laser therapy or Nd:YAG laser treatment has been found to improve local pain in myofascial pain syndrome [23, 24].
- Ultrasound (continuous mode 1.25–1.5 w/cm^{2j}) applies mechanical and thermal energy to skin and underlying tissue. It can temporarily decrease the pain and discomfort of active TrPs [25, 26].
- Transcutaneous electrical nerve stimulation (TENS) employing pulse duration of 100–110uS/frequency at 70–80 HZ for 25 minutes has been used with some success in patients with MPS [27, 28]. It can improve the spontaneous pain but not the pressure-induced pain [29]
- Dry needling inserts needles directly into the TrPs. It supposedly acts upon cutaneous nociceptive delta-A fibers. In two double-blind, placebo-controlled studies [30, 31], dry needling of TrPts in myofascial pain syndrome resulted in short-term relief (1–4 weeks) of pain and improved performance of daily activities ($P < 0.0.5$). Another open and prospective study found a positive effect of dry needling comparable to physical therapy in deactivation of trigger points [32].

As described above, different modalities of nonpharmacological treatment have been studied for alleviating pain in myofascial pain. The main limitation of these approaches, despite some encouraging results, is the short duration of their analgesic effect.

The pharmacological approach for treatment of MPS encompasses a large number of agents used either alone or more often in combination. These include nonsteroidal, anti-inflammatory drugs (NSAID), muscle relaxants, antidepressants, and antiepileptic analgesic agents. Lidocaine patches have fewer side effects and can relieve local pain at TrPTs. Trigger point injections with anesthetic agents and steroids injections are sometimes used in recalcitrant cases. Despite the availability of a wide range of treatment modalities for deactivation of trigger points in MPS, it is generally believed that current strategies offer only transient pain relief [33, 34]. Considering the short duration and side effects of current nonpharmacological and pharmacological treatments of MPS, novel therapeutic modalities with acceptable

safety profile and infrequent side effects are needed to provide more sustained relief and better acceptance by the patients.

BoNT Treatment of Myofascial Pain Syndrome (MPS)

With increasing recognition of the analgesic effects of BoNTs in human subjects [35], there is a high level of interest among clinicians in academic and nonacademic settings to explore this mode of therapy for alleviating muscle pain including the pain of myofascial pain syndrome. The interest in the analgesic effects of botulinum toxins in human pain disorders and myofascial pain, in particular, is reflected in several reviews published on this subject recently [36–43].

Double-Blind, Placebo-Controlled Studies

Cheshire et al. were first to suggest the efficacy of onabotulinumtoxinA (onaA) in myofascial pain syndrome based on a small double-blind, cross-over study [44]. Six patients (4 women), 35–50 years of age, participated in and completed the eight-week-duration study. Compared to saline, patients who had injections of onaA into the trigger points of trapezius and cervical paraspinal muscles showed significant ($P < 0.05$) reduction of pain (using VAS) and perception of unpleasantness (by patient account) at two, four, and eight weeks. The dose of onaA was 50 units diluted in 4cc of normal saline, equally divided between two to three sites. Since this early observation, 14 more double-blind, placebo-controlled studies have been published on the efficacy of BoNT-A in myofascial pain syndrome meeting the class I and class II study criteria set forth by the American Academy of Neurology [45, 46] [Table 8.2]. Five of these 14 studies meet the class I criteria. The details of four of the class I studies with 100 or more patients are presented in this chapter. A summary of data from other blinded studies is presented in Table 8.2.

In 2005, Ferrante et al. [57] conducted a double-blind, placebo-controlled, single center study on 132 patients with myofascial pain syndrome affecting the cervicothoracic region. Two weeks before treatment, the study subjects were gradually taken off their pain medications and were put on a new regimen that included amitriptyline (10–75 mg, daily), ibuprophen 800 mg every 6 hours, and propoxyphene/acetaminophene as a rescue drug. The subjects were randomized into four groups: three groups received different doses of onaA and one group received saline. For the toxin groups, investigators injected 10, 25, and 50 units up to 5 trigger points. Patients with more than five trigger points were excluded from the study. Injections were done through a 22 gauge needle. Pain relief and quality of life were assessed by VAS, pain algometry (measuring pain threshold), and SF36 health survey as quality of life measure at 1, 2, 4, 6, and 12 weeks after injection. The investigators found no significant differences between the three toxin groups and placebo in

Table 8.2 Randomized data from clinical trials of botulinum toxin treatment in myofascial pain syndrome (MFPS). The table only includes double-blind, placebo-controlled, class I, and class II studies

Authors and year	# Pts	Study design, class	Toxin	Dose in units	Location of myofascial pain	Outcome measures	Results
Canales et al., 2020 [47]	100	DB/PC, Parallel; Class I	onaA	Ona A: 3 groups, Temporal: 10,20,25 Massater: 30,50,75 Group 4: Oral appliance (OA) Group 5: Saline	Temporal Masseter	Primary: VAS: for pain; PPT: pressure pain threshold; Secondary: masseter thickness in ultrasound	All 3 onaA groups showed significant reduction of VAS score compared to saline from day 7 to the end of study. onaA and OA had same efficacy after day 14. PPT increased in OnaA group compared to saline and OA groups ($P < 0.01$).
Dessie et al., 2019 [48]	60	DB/ PC; Parallel; Class II	onaA	200 units of onaA versus 10cc of saline	Pelvic floor	Pain change (on palpation)-measured by VAS at 4 and 12 weeks, GIII: measured at 4 & 12 weeks	More patients in onaA group reported pain relief and satisfaction with treatment. GIII change was significant for onaA at wk4 ($P = 0.03$).
Kwanchuay et al., 2015 [49]	33	DB/PC; Parallel; Class II	OnaA	20 u of onaA and saline (02cc) injected into 24 TrPs	Upper trapezius, multiple TrP injections	VAS and PPT at 3 and 6 weeks	-VAS: Both onaA and placebo showed significant improvement from baseline at 6 weeks. -Increase in PPT (compared to baseline) was only significant for onaA (0.036).

(continued)

Table 8.2 (continued)

Authors and year	# Pts	Study design, class	Toxin	Dose in units	Location of myofascial pain	Outcome measures	Results
Nicol et al., 2014 [50]	57	Two steps: First, open label 114 pts; Second, DB/PC; Parallel; Class I in 57 of Responders	BoNT-A Fixed pattern with variable injection paradigm	12.5–50 units per muscle, total dose not exceeding 300 units	Neck and shoulder muscles	VAS: two grades or 30% pain relief; BPI SF-36	First injection- open label, 114 pts, 50% responded Second injection- (DB/PC) in 57 responders. Two weeks into the blinded study, VAS improved, compared to baseline ($P = 0.019$); general activity, sleep, headaches also improved: Ps = 0.046, 0.02, 0.04, respectively.
Benecke et al., 2011 [51]	154	DB/PC; Parallel; Class I	aboA	Fixed dose- 40u per TrPTs, 10 TrPTs injected	Neck and shoulder	Proportion of patients with mild or no pain at wk 5. Secondary: PGA (patient & physician), pain duration	-Duration of daily pain reduced in wks 9 and 10 (both $P = 0.04$) but not wk 5. -Patient and physician global assessment favored aboA at wks 8 & 12.
De Andres et al., 2011 [52]	27	DB/PC; Parallel; Class II	OnaA was injected in one side, saline on the other side	50 units into IP and QL muscles	Lumbar region	VAS, ADL, anxiety, depression assessment	A trend in VAS improvement ($P = 0.054$) on the side injected by onaA.

(continued)

Table 8.2 (continued)

Authors and year	# Pts	Study design, class	Toxin	Dose in units	Location of myofascial pain	Outcome measures	Results
Lew et al., 2008 [53]	29	DB/PC; Parallel; II	OnaA	50 units per injection site total not > 200	Neck and shoulder	VAS: pain NDI SF-36: for activity of daily living (ADL)	VAS: improved at 2 and 4 months (P < 0.025) SF-36 mental health: trend at months 2 & 4 wks ($P = 0.09$) in favor of onaA.
Gobel et al., 2006 [54]	145	DB/PC; Parallel; Class I	AboA	40 units into 10 most tender trigger points	Neck and shoulder	Proportion of patients with mild or no pain in VAS	At wk 5 post injection, 51% in aboA group and 26% in saline group reported mild or no pain ($P = 0.002$).
Qerama et al., 2006 [55]	30	DB/PC; Parallel; class II	onaA	50 units-single injection into infra-spinatus	Shoulder/ upper back	VAS: pain measured at days 3 and 28	VAS: No difference between onaA and saline, both injections showed >30% improvement compared to baseline score.
Ojala et al., 2006 [56]	31	DB-PC; Cross-over; class II	onaA	5 units into TrPs; Total dose= 15–35 units	Neck and shoulder	VAS: for pain; PPT	OnaA and saline both improved neck pain and PPT. No difference (statistically) between the two.
Ferrante et al., 2005 [57]	132	DB-PC; Parallel; Class I	onaA	10,25,50 units into TrPTs up to 5 TrPT; Maximum dose =250	Cervico-thoracic	VAS:pain; Pain algometry; SF-36; all tested over 12 weeks	No improvement of myofascial pain after onaA injection.

(continued)

Table 8.2 (continued)

Authors and year	# Pts	Study design, class	Toxin	Dose in units	Location of myofascial pain	Outcome measures	Results
Wheeler et al., 2001 [58]	50	DB/PC; Parallel; Class II	onaA	Multiple trigger points; Mean total dose = 231 units	Cervico-thoracic	Pain; algometry; PGAP; SF-36; all assessed at 0,4,8,12,16 weeks	onaA and saline injections improved all outcome measures (except SF-36). No difference between the two treatments.
Freund and Schwartz, 2000 [59]	28	DB/PC; Parallel; Class II	onaA	Five trigger points; were injected with 100 units	Neck and shoulder	VAS: pain; NRM	VAS improved two weeks post onaA injection ($P < 0.02$). NRM improved 4 weeks after onaA injection.
Wheeler et al., 1998 [60]	33	DB/PC; Parallel; Class II	onaA	Single trigger point either 50 or 100 units	Cervico-thoracic	Pressure algometry, PGAP, NPDS	Both onaA and saline significantly improved pain. Statistically, no difference between the two treatments.

onaA onabotulinumtoxinA(Botox), *aboA* AbobotulinumtoxinA(dysport), *GIII* global impression improvement index, *BPI* Brief pain inventory, *NS* not significant, *NDI* neck disability index, *PPT* pressure pain threshold, *NRM* neck range of motion, *PGAP* patient global assessment of pain, *NPDS* Neck and pain disability scale, *TrPT* trigger point, *OA* oral appliance, *ADL* activity of daily living

regard to VAS scores, pressure algometry, SF-36 values, and the use of rescue drugs. However, in all four groups, including the placebo group, patients reported significant improvement of their pain (assessed by VAS and pain algometry) and in using less rescue medication(s) compared to their baseline values before treatment ($P < 0.001$). Some subsets of SF-36 questionnaire, when compared between toxin and placebo group, demonstrated improvements in favor of the toxin group; these subsets included role emotional subscale ($P < 0.05$), vitality ($P = 0.053$), and social functioning ($P = 0.057$). Three patients in the toxin group developed a transient flu-like reaction.

In 2006, Gobel et al. conducted a well-designed, double-blind, placebo-controlled, multicenter study on 145 subjects who had moderate to severe pain affecting the neck and shoulder muscles [54]. Injections of saline or aboA (40 units per point) were made into the 10 most tender trigger points. The primary outcome was the proportion of patients with mild or no pain at week 5 compared to baseline.

At week 5, significantly more patients in the aboA group reported mild or no pain compared to the patients in the placebo group (51% versus 26%; $P = 0.002$). Compared to placebo, aboA injections resulted in significantly greater change from baseline in pain intensity during weeks 5–8 ($P < 0.05$) and significantly more days per week without pain between weeks 5–12 ($P = 0.036$). The treatment was well tolerated. Side effects were mild and were resolved within eight weeks.

Benecke et al. [51] performed a prospective, double-blind, placebo-controlled, multi-center study with aboA on 153 patients with neck and shoulder myofascial pain syndrome. Patients had moderate to severe pain affecting neck and shoulder muscles. Their disease duration was 6–24 months. Their study had the same inclusion and exclusion criteria and same toxin dose criteria (40 units/trigger point, 10 trigger points injected, a total dose of 400 units) as the study of Gobel et al. [50]. However, unlike that study, they used a fixed injection-site design; the injections were done into predetermined areas of the muscles; four injection sites (2 injections per side) for trapezius muscle, four injection sites (2 per side) for neck paraspinal muscles, and two injections for temporalis muscle (1 per side).

The primary outcome of the study was the proportion of patients with no pain or mild pain at week 5 post-injection. Secondary outcomes consisted of changes in pain intensity and the number of pain-free days per week. At week 5, 49% (37/76) of patients in the aboA group and 38% (27/72) of patients in the saline group responded to treatment ($P = 0.1873$). However, duration of daily pain was reduced more in the aboA group compared to the placebo group from week 5 post-injection demonstrating significant differences in favor of aboA at week 9 and week 10 (P value was 0.04 for both weeks). The treatment was well tolerated. No significant side effects were reported.

Recently, in another double-blind, placebo-controlled class 1 study [47], the effect of onabotulinumtoxinA injection into temporalis and masseter muscles was compared with placebo (saline) and oral appliance in 100 patients with myofascial pain involving these muscles. Patients were divided into five groups, each containing 20 individuals. The first three groups received onaA injections with three different doses. Patients in the low dose group were injected with 10 units into temporalis and 25 units into masseter. Those in the medium dose group received 15 units into temporalis and 50 units into masseter, and the individuals in the high dose group were given 200 units into temporalis and 75 units into masseter. Group 4 was treated with oral appliance and group 5 (placebo group) received normal saline in a volume comparable with onaA. Primary outcome measures consisted of VAS for pain and pain pressure threshold (PPT). Secondary outcomes included masticatory performance and measurement of muscle thickness. When compared to saline, VAS pain scores decreased significantly from day 7 to the end of study (week 24) in the three onaA groups ($P < 0001$). Oral appliance did the same thing, but after day 14. In all three onaA groups, patient pain threshold increased significantly ($P < 0.01$) compared to both the placebo and oral appliance groups. A transient decline in masticatory performance ($P < 0.05$) and muscle contraction ($P < 0.0001$), as well as a decrease in muscle thickness ($P < 0.05$) were found as dose-related adverse effects of BoNT-A. Since both low dose and high dose of onaA demonstrated the same efficacy, the authors recommended using low dose to avoid side effects.

Comparator Studies

In a blinded and crossover study, Graboski et al. [61] compared the efficacy of onaA injection into trigger points (25 units/point and up to 8 points) with anesthetic bupivacaine (0.5%) and dry needling in 18 patients with MPS. Both modes of therapy significantly reduced pain compared to baseline ($P = 0.006$), but no significant difference between the two was noted as to the degree of pain control. Dry needling did not alleviate pain. The duration of action was also approximately the same (4 weeks) for both onaA and the anesthetic agent; there was a trend, however, in favor of onaA having a longer duration of effect. Authors found the substantially higher cost of BoNT treatment ($500 for onaA vs. $1 for bupovacaine) prohibitive to recommend it for routine use in MFPS. These results agree with the observations of Kamanli et al. [62] who, in a single blind study, compared the effect of lidocaine with onaA and dry needling in 78 patients with MPS. At four weeks, the effects of onaA and lidocaine in pain relief were compared, both markedly reduced pain ($P < 0.005$).

In a recent randomized single blind study [63], the effect of botulinumtoxinA injection was compared with acupuncture and saline in 54 patients with temporomandibular myofascial syndrome. The toxin, onabotulinumtoxinA was injected into masseter (30 units) and temporalis muscles (10 units). In the acupuncture group, patients received four sessions of traditional acupuncture for one month (one session per week), each session lasting 20 minutes. The primary outcomes were level of pain measured by VAS and pressure pain threshold (PPT). Patients were evaluated once, one month after injections. One month after injection, both onaA and acupuncture reduced the pain significantly compared to saline injection ($P < 0.01$). There was no difference between the onaA and acupuncture groups with regard to level of pain reduction. Significant improvement of PPT was noted only in botulinum toxin group and in both muscles, however ($P = 0.001$).

Case Reports

Patient (8-1): Myofascial Pain Syndrome with Two Trigger Points in One Muscle

A 38-year-old gentleman, a busy and successful surgeon, complained of localized pain in the left upper back for the past five years. He had a 10-year history of competitive wrestling during his younger years through which he supported his schooling. The pain was localized to the left infrascapular region and was both spontaneous and exercise-induced. The area was sensitive to touch and upon pressing caused referred pain radiation toward the lower part of the scapula. The pain was described as aching and deep, but at times also had a burning quality. On examination, two trigger points could be identified in the upper subscapular region; pressing upon them induced referred pain.

After discussing the possible side effects of BoNT therapy, 20 units of onabotulinumtoxinA were injected into each trigger point (Fig. 8.1). Within one week, the

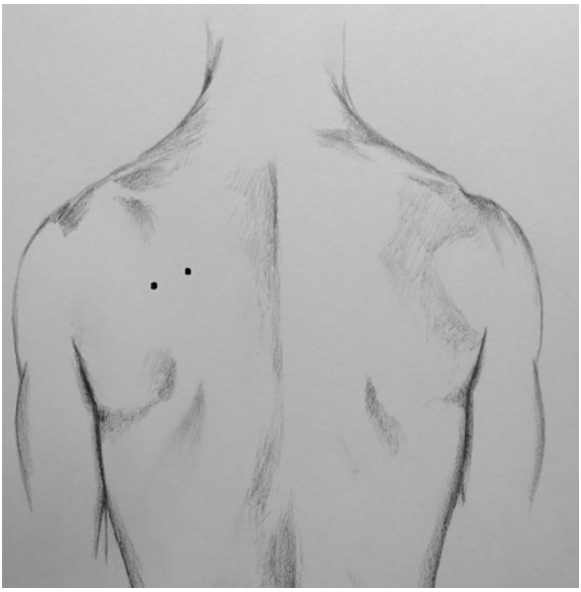

Fig. 8.1 Points of injection in Patient 8-1. Each site was injected with 20 units of onabotulinumtoxinA (Botox), 40 units total

patient reported marked reduction of his pain (a change in VAS from 8 to 1). He required reinjections every six months that produced the same satisfactory response over a follow-up period of three years.

Patient (8-2): Multiple Trigger Points in Multiple Muscles

A 62-year-old gentleman, a construction worker, developed neck, shoulder, and upper back pain gradually increasing in intensity over the past two years. His past medical history was significant for an episode of tetanus that followed a foot injury 12 years ago. He was aggressively treated for tetanus and recovered. For his current pain problem, his medications consisted of gabapentin, tramadol, and lidocaine patch applied daily. He was not satisfied with the level of pain control, however. The muscle pain interfered with his daily activities and kept him up at night. On examination, there were a number of trigger points scattered within the right trapezius, deltoid, splenius capitis, as well as the supra- and infra-scapular muscles identified by thumb pressure and induction of referred pain.

OnabotulinumtoxinA was injected into 20 trigger points located in the aforementioned muscles. The dose per trigger point was 20 units with a total dose of 400 units per session. Patient reported significant reduction of pain with a 6 points reduction in VAS (baseline VAS of 8–9 changed to 2–3) within two weeks. The patient was satisfied with the BoNT therapy that had made his pain bearable. No side effects were noted over the six years of treatment with multiple trigger point injections every three to four months. Continuous, periodic OnabotulinumA injections remained effective over six years.

Comment on the Efficacy of BoNT Therapy in Myofascial Pain Syndrome

Critically reviewing the data from the five high-quality class I studies on myofascial pain syndrome and from comparative studies, I believe that BoNT therapy with type A toxin is effective in most patients who suffer from this form of chronic pain. The multicenter, flexible design study of Gobel et al. [54], where large areas of the muscles were injected (10 trigger points), abobotulinumtoxinA (aboA) was significantly more effective than saline in reducing muscle pain at week 5 (the primary outcome point of the study). The multicenter study of Benecke et al. [51] with fixed injection site design failed to show significant pain relief at week 5 but did show significant reduction of pain after aboA injection at weeks 8 and 10. Canales et al. [47] demonstrated that onabotulinumtoxinA relieves myofascial pain (assessed by VAS) and increases pain threshold of temporomandibular area from day 7 to day 26 after injection. The study of Ferrante et al. [57] from UCLA failed to show a statistically meaningful difference between onaA and saline injection (although both were highly effective) in myofascial pain syndrome. This negative result may have two explanations which are not mutually exclusive: (1) authors injected into a small area of the muscles with injections limited to 5 or less trigger points. (2) The study showed that saline is as effective as onabotulinumtoxinA in treatment of myofascial pain syndrome. When both the trial drug and placebo (saline) are highly effective and similar in term of effectiveness, the most likely possible conclusion is that the study showed a large placebo effect precluding proper assessment of BoNT efficacy [64]. This issue has been the case in some other negative class II studies cited in Table 8.2 [55, 58, 60]. In a recent study from UCLA [50], authors found botulinum toxin injections significantly alleviated pain in MFPS, at the same time improving patients' daily activities, headaches, and depression. They attributed the failure of their previous study [57] to their injection pattern that included only a few trigger points.

The dose per trigger point is another factor that can influence the results. While most studies used a dose of 20 units of onaA and 40–50 units of aboA per trigger point, one failed class II study used only 5 units of onaA per trigger point [56] [Table 8.2].

The comparative studies cited above also uniformly showed effectiveness of BoNT-A in treatment of myofascial pain syndrome [61–63]. These studies claim that anesthetic agents, acupuncture, and laser are as effective as BoNT-A in short-term treatment of MPS. Blinded, long-term comparative studies are not available which would likely favor BoNT treatment because of its long-term effect.

There is a need for a large multicenter study that is modeled after an already published and successful class I multicenter study, such as that of Gobel et al. [54]. Positive results from such a study would promote FDA approval of botulinum toxinA (aboA) for treatment of myofascial pain syndrome, ultimately offering help to a large number of patients affected by this chronic pain disorder.

The Mechanism of Action of BoNTs in Myofascial Pain Syndrome (MPS)

The reported analgesic effect of BoNTs reported in patients with myofascial pain syndrome probably results from different mechanisms working at different levels of pain pathways. As described above, under the pathophysiology of MPS, acetylcholine is increased locally in the taut muscle bands of the trigger points and its high level contributes to hypersensitivity of muscle fibers, muscle twitch, and muscle contraction. Botulinum neurotoxins block the release of acetylcholine at the neuromuscular junction. The extracellular fluid around the trigger points contains elevated levels of pain mediators (Substance P and CGRP) and inflammatory markers such as cytokines [11, 12]. It has been shown, in animal models, that botulinum toxins inhibit the release of pain mediators such as Substance P and calcitonin gene-related peptide at peripheral and spinal cord levels [66, 67]. Furthermore, an anti-inflammatory effect has been shown for BoNTs in formalin model of pain where pretreatment with onabotulinumtoxinA blocks the inflammatory peak of pain and reduces the accumulation of glutamate in the tissue that follows the formalin injection [68].

It has been shown, by immunofluorescent technique, that cleaved SNAP 25, the target molecule of BoNT-A—after peripheral injection of the toxin—travels rostrally to the dorsal root ganglia and affects the first-order sensory neurons [69]. Further evidence for central analgesic effects of BoNT-A comes from painful experimental diabetic neuropathy induced by injection of paclitaxel and streptozotocin agents. In both cases, unilateral injection of the toxin improves bilaterally developed painful neuropathy [70, 71]. In chronic myofascial pain syndrome with developed central sensitization, the analgesic effects of botulinum toxinA could be partly related to its inhibiting effect upon intrafusal muscle fibers that, through their large input to the spinal cord, enhance central sensitization [72]. The peripheral and central mechanisms involved in the analgesic effects of botulinum toxins were recently detailed by Lackovic [73, 74].

Fibromyalgia

Fibromyalgia is a common clinical condition which affects 2%–3% of the US population [75, 76]. The cardinal feature of the disease is chronic diffuse body pain. Patients often have additional symptoms of fatigue, headaches, mood disorders, sleep disturbance, and bowel disorders. Some patients demonstrate evidence of impairment of hypothalamic–pituitary–adrenal axis. Increased level of excitatory neurotransmitters (including substance P) and reduction of other biogenic amines found in patients with fibromyalgia suggest that some symptoms of fibromyalgia are related to chronic central sensitization [77]. Some patients complain of dry eyes, dyspnea, dysphagia, and palpitation. Paresthesias in the limbs are not uncommon.

A large number of medications have been tried to alleviate the pain of fibromyalgia. Pregabalin, duloxetine, milnacipran, and amitriptyline are currently used as first-line drugs for treatment of fibromyalgia, but their effect is modest [78]. According to the current criteria of ACR, the diagnostic criteria of fibromyalgia are met if a patient demonstrates all three criteria described below:

1. Widespread pain index (WPI) of 7 and symptom severity (SS) scale score of 5, or if WPI equals 3–6 and SS scale score equals to 9.
2. Presence of this symptomatology for at least three months.
3. The patient does not have any other disorder that can explain the pain [79].

Botulinum Toxin Treatment of Fibromyalgia

The published literature on the efficacy of BoNTs in fibromyalgia is very limited. There are no published blinded and placebo-controlled studies in this area. The literature is limited to two letters to the editor and one retrospective study [80–82].

Paulson and Gill [80] compared the effects of onaA (100 units) with that of lidocaine (0.5%) in 10 patients with fibromyalgia. They used a baseline fibromyalgia questionnaire to measure pain, disability, medication intake, and routine daily activities. The patients first received lidocaine followed by injection with BoNT. None of the patients who received BoNT injections into the trigger points showed any improvement.

In another small open observation [81], 16 patients who met the clinical criteria of fibromyalgia were injected with onaA (100 units) into multiple trigger points. Five patients had one trigger point injection, seven had two, while the remaining four patients had three and four trigger point injections. The authors reported significant improvement of pain in all patients. Pain relief lasted for 16 weeks after each type of injection. The method of assessing pain improvement and the exact dose per trigger point were not mentioned in the communication, however.

In the most recent study [82], 66 patients with fibromyalgia (96.9% females) were divided into three groups. Group 1 received BoNT-A into trigger points of cervical muscles, group 2 underwent problem-solving therapy, and group 3 had both therapies. Comparing the response of the three groups, authors reported that pain improved in 31.8% of the toxin group, 13.6% of the problem-solving group, and 22.7% of the group that received both therapies, respectively.

Comment

The role of BoNT treatment in fibromyalgia has not been assessed by controlled studies. Using the efficacy criteria of the assessment and development committee of the American Academy of Neurology [45, 46], the level of efficacy of BoNTs in

fibromyalgia is undetermined due to lack of high-quality studies. Given the diffuse and often poorly localized nature of the pain, along with the complexity of symptomatology of fibromyalgia, it is unlikely that BoNT treatment would be effective in this disorder.

References

1. Weller JL, Comeau D, Otis JAD. Myofascial pain. Semin Neurol. 2018;38(6):640–3. https://doi.org/10.1055/s-0038-1673674. Epub 2018 Dec 6. PMID: 30522139
2. Celik D, Mutlu EK. Clinical implication of latent myofascial trigger point. Curr Pain Headache Rep. 2013;17:353.
3. Simons DR, Travell J, Simons L. Myofascial pain and dysfunction: the trigger point manual, vol. 1. 2nd ed. Baltimore: Williams & Wilkins; 1999. p. 23–34.
4. Gerwin RD, Shannon S, Hong CZ, Hubbard D, Gervitz R. Inter-rater reliability in myofascial trigger point examination. Pain. 1997;69:65–73.
5. Fricton JR, Kroening R, Haley D, Siegert R. Myofascial pain syndrome of the head and neck: a review of clinical characteristics of 164 patients. Oral Surg Oral Med Oral Pathol. 1985;60:615–23.
6. Gerwin RD. Classification, epidemiology, and natural history of myofascial pain syndrome. Curr Pain Headache Rep. 2001;5:412–20.
7. Han SC, Harrison P. Myofascial pain syndrome and trigger-point management. Reg Anesth. 1997;22:89–101.
8. Simons DG, Hong CZ, Simons SL. Endplate potentials are common to midfiber myofascial trigger points. American Journal of Physical Medicine and Rehabilitation. 2002;81:212–22.
9. Ferguson LW, Gerwin R. Clinical mastery in the treatment of myofascial pain. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
10. Desai MJ, Bean MC, Heckman TW, Jayaseelan D, Moats N, Nava A. Treatment of myofascial pain. Pain Manag. 2013;3(1):67–79. https://doi.org/10.2217/pmt.12.78. PMID: 24645933.
11. Shah PJ, Phillips TM, Danoff JV, Gerber LH. An in vivo microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. J Appl Physiology. 2005;99:1977–84.
12. Shah JP, Danoff JV, Desai MJ, Parikh S, Nakamura LY, Phillips TM, et al. Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. Arch Phys Med Rehabil. 2008;89:16–23.
13. Aoki KR, Francis J. Updates on the antinociceptive mechanism hypothesis of botulinum toxin A. Parkinsonism Relat Disord. 2011;17(Suppl 1):S28–33.
14. Climent, Kuan TS, Fenollosa P, Martin-Del-Rosario F. Botulinum toxin for the treatment of myofascial pain syndromes involving the neck and back: a review from a clinical perspective. Evid Based Complement Alternat Med. 2014; EPub Ahead of print
15. Mazza DF, Boutin RD, Chaudhari AJ. Assessment of myofascial trigger points via imaging: a systematic review. Am J Phys Med Rehabil. 2021; https://doi.org/10.1097/PHM.0000000000001789. Epub ahead of print. PMID: 33990485
16. Bordoni B, Sugumar K, Varacallo M. Myofascial pain. 2021 Jun 20. In: StatPearls [Internet]. Treasure Island StatPearls Publishing; 2021 Jan–. PMID: 30570965.
17. Travell J, Rinzler SH. The myofascial genesis of pain. Postgrad Med. 1952;11(5):425–34. https://doi.org/10.1080/00325481.1952.11694280. PMID: 14920327.
18. Fernández-de-Las-Peñas C, Dommerholt J. International consensus on diagnostic criteria and clinical considerations of myofascial trigger points: a delphi study. Pain Med. 2018 Jan 1;19(1):142–50.

19. Boonruab J, Poonsuk P, Damjuti W, Supamethangkura W. Myofascial pain syndrome focused on the upper trapezius muscle: a comparative randomized controlled trial of the court-type traditional thai massage versus the Thai Hermit. J Evid Based Integr Med. 2021;26:2515690X211030852. https://doi.org/10.1177/2515690X211030852. PMID: 34293959.
20. Travell JG, Simons DG. Apropos of all muscles. In: Travell JG, Simons DG, editors. Myofascial pain and dysfunction, vol. 1. Baltimore: Williams & Wilkins; 1992.
21. Esenyel M, Caglar N, Aldemir T. Treatment of myofascial pain. Am J Phys Med Rehabil. 2000;79:48–52.
22. Sun MY, Hsieh CL, Cheng YY, Hung HC, Li TC, Yen SM, Huang IS. The therapeutic effects of acupuncture on patients with chronic neck myofascial pain syndrome: a single-blind randomized controlled trial. Am J Chin Med. 2010;38:849–59.
23. Uemoto L, Nascimento de Azevedo R, Almeida Alfaya T, Nunes Jardim Reis R, Depes de Gouvêa CV, Cavalcanti Garcia MA. Myofascial trigger point therapy: laser therapy and dry needling. Curr Pain Headache Rep. 2013;17(357)
24. Alayat MS, Battecha KH, ELsodany AM, Ali MI. Pulsed ND:YAG laser combined with progressive pressure release in the treatment of cervical myofascial pain syndrome: a randomized control trial. J Phys Ther Sci. 2020;32(7):422–427. https://doi.org/10.1589/jpts.32.422. Epub 2020 Jul 3. PMID: 32753780; PMCID: PMC7344286.
25. Blikstad A, Gemmell H. Immediate effect of activator trigger point therapy and myofascial band therapy on non-specific neck pain in patients with upper trapezius trigger points compared to sham ultrasound: a randomized controlled trial. Clin Chiropr. 2008;11:23–9.
26. Srbely JZ, Dickey JP, Lowerison M, Edwards AM, Nolet PS, Wong LL. Stimulation of myofascial trigger points with ultrasound induces segmental antinociceptive effects: a randomized controlled study. Pain. 2008;139:260–6.
27. Santiesteban AJ. Physical agents and musculocutaneous pain. In: Gould III JA, Davies GJ, editors. Orthopaedic and sports physical therapy, vol. 2. St. Louis: Mosby; 1985. p. 199–211.
28. Rachlin ES. Trigger point management. In: Rachlin ES, editor. Myofascial pain and Fibromyalgia. St. Louis: Mosby; 1994. p. 173–95.
29. Hernandez JVL, Calvo-Lobo C, Zugasti AM, Fernandez-Carnero J, Beltran Alacreu H. Effectiveness of dry needling with percutaneous electrical nerve stimulation of high frequency versus low frequency in patients with myofascial neck pain. Pain Physician. 2021;24(2):135–143 PMID: 33740346.
30. Tekin L, Akarsu S, Durmuş O, Cakar E, Dinçer U, Kıralp MZ. The effect of dry needling in the treatment of myofascial pain syndrome: a randomized double-blinded placebo-controlled trial. Clin Rheumatol. 2013;32:309–15.
31. Pai MYB, Toma JT, Kaziyama HHS, Listik C, Galhardoni R, Yeng LT, Teixeira MJ, Ciampi de Andrade D. Dry needling has lasting analgesic effect in shoulder pain: a double-blind, sham-controlled trial. Pain Rep. 2021;6(2):e939. https://doi.org/10.1097/PR9.0000000000000939. PMID: 34235343; PMCID: PMC8240781.
32. Rayegani SM, Bayat M, Bahrami MH, Raeissadat SA, Kargozar E. Comparison of dry needling and physiotherapy in treatment of myofascial pain syndrome. Clin Rheumatol. 2014;33(6):859–64. https://doi.org/10.1007/s10067-013-2448-3. Epub 2013 Dec 19. PMID: 24352752.
33. Desai MJ, Shkolnikova T, Nava A, Inwald D. A critical appraisal of the evidence for botulinum toxin type a in the treatment for cervico-thoracic myofascial pain syndrome. Pain Pract. 2014;14:185–95.
34. Zhou JY, Wang D. An update on botulinum toxin a injections of trigger points for myofascial pain. Curr Pain Headache Rep. 2014;386:1–5.
35. Jabbari B. Botulinum neurotoxins in the treatment of refractory pain. Nat Clin Pract Neurol. 2008;4(12):676–85. https://doi.org/10.1038/ncpneuro0948. PMID: 19043424.
36. Jabbari B, Machado GD. Treatment of refractory pain with botulinum toxins: an evidence-based review. Pain Med. 2011;12:1594–606.

37. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes: an evidence-based review. Toxicon. 2018;147: 120–128. https://doi.org/10.1016/j.toxicon.2018.01.017. Epub 2018 Feb 1. PMID: 29409817.
38. Park J, Park HJ. Botulinum toxin for the treatment of neuropathic pain. Toxins (Basel). 2017;9(9):260. https://doi.org/10.3390/toxins9090260. PMID: 28837075; PMCID: PMC5618193.
39. Mittal SO, Safarpour D, Jabbari B. Botulinum toxin treatment of neuropathic pain. Semin Neurol. 2016;36(1):73–83. https://doi.org/10.1055/s-0036-1571953. Epub 2016 Feb 11. PMID: 26866499.
40. Ray JC, Hutton EJ, Matharu M. OnabotulinumtoxinA in migraine: a review of the literature and factors associated with efficacy. J Clin Med. 2021;10(13):2898. https://doi.org/10.3390/jcm10132898. PMID: 34209849; PMCID: PMC8269087.
41. Lakra C, Cohen H. A clinical review of the use of botulinum toxin type A in managing central neuropathic pain in patients with spinal cord injury. J Spinal Cord Med. 2020:1–5. https://doi.org/10.1080/10790268.2020.1848278. Epub ahead of print. PMID: 33263489.
42. Egeo G, Fofi L, Barbanti P. Botulinum neurotoxin for the treatment of neuropathic pain. Front Neurol. 2020;11:716. https://doi.org/10.3389/fneur.2020.00716. PMID: 32849195; PMCID: PMC7431775.
43. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459. PMID: 31387301; PMCID: PMC6723487.
44. Cheshire WP, Abashian SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. Pain. 1994;59:65–9.
45. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology. 2008;71(20):1639–1643. https://doi.org/10.1212/01.wnl.0000336535.27773.c0. PMID: 19001255.
46. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008;71(20):1634–1638. https://doi.org/10.1212/01.wnl.0000336533.19610.1b. PMID: 19001254.
47. De la Torre Canales G, Alvarez-Pinzon N, Muñoz-Lora VRM, Vieira Peroni L, Farias Gomes A, Sánchez-Ayala A, Haiter-Neto F, Manfredini D, Rizzatti-Barbosa CM. Efficacy and safety of botulinum toxin type A on persistent myofascial pain: a randomized clinical trial. Toxins (Basel). 2020;12(6):395. https://doi.org/10.3390/toxins12060395. PMID: 32549196; PMCID: PMC7354430.
48. Dessie SG, Von Bargen E, Hacker MR, Haviland MJ, Elkadry E. A randomized, double-blind, placebo-controlled trial of onabotulinumtoxin A trigger point injections for myofascial pelvic pain. Am J Obstet Gynecol. 2019;221(5):517.e1–517.e9. https://doi.org/10.1016/j.ajog.2019.06.044. Epub 2019 Jun 27. PMID: 31254522.
49. Kwanchuay P, Petchnumsin T, Yiemsiri P, Pasuk N, Srikanok W, Hathaiareerug C. Efficacy and safety of single botulinum toxin type A (Botox®) injection for relief of upper trapezius myofascial trigger point: a randomized, double-blind, placebo-controlled study, J Med Assoc Thai. 2015;98(12):1231–6. PMID: 27004309.
50. Nicol AL, Wu II, Ferrante FM. Botulinum toxin type a injections for cervical and shoulder girdle myofascial pain using an enriched protocol design. Anesth Analg. 2014;118(6):1326–35. https://doi.org/10.1213/ANE.0000000000000192. PMID: 24842179; PMCID: PMC4030686.
51. Benecke R, Heinze A, Reichel G, Hefter H, Göbel H. Dysport myofascial pain study group. Botulinum type A toxin complex for the relief of upper back myofascial pain syndrome: how do fixed-location injections compare with trigger point-focused injections? Pain Med. 2011;12(11):1607–14. https://doi.org/10.1111/j.1526-4637.2011.01163.x. Epub 2011 Jun 21. PMID: 21692970.
52. De Andrés J, Adsuara VM, Palmisani S, Villanueva V, López-Alarcón MD. A double-blind, controlled, randomized trial to evaluate the efficacy of botulinum toxin for the treatment of

lumbar myofascial pain in humans. Reg Anesth Pain Med. 2010;35(3):255–60. https://doi.org/10.1097/AAP.0b013e3181d23241. PMID: 20921836.
53. Lew HL, Lee EH, Castaneda A, Klima R, Date E. Therapeutic use of botulinum toxin type A in treating neck and upper-back pain of myofascial origin: a pilot study. Arch Phys Med Rehabil. 2008;89(1):75–80. https://doi.org/10.1016/j.apmr.2007.08.133. PMID: 18164334.
54. Göbel H, Heinze A, Reichel G, Hefter H, Benecke R; Dysport myofascial pain study group. Efficacy and safety of a single botulinum type A toxin complex treatment (Dysport) for the relief of upper back myofascial pain syndrome: results from a randomized double-blind placebo-controlled multicentre study. Pain. 2006;125(1-2):82–8. https://doi.org/10.1016/j.pain.2006.05.001. Epub 2006 Jun 5. PMID: 16750294.
55. Qerama E, Fuglsang-Frederiksen A, Kasch H, Bach FW, Jensen TS. A double-blind, controlled study of botulinum toxin A in chronic myofascial pain. Neurology. 2006;67(2):241–5. https://doi.org/10.1212/01.wnl.0000224731.06168.df. PMID: 16864815.
56. Ojala T, Arokoski JP, Partanen J. The effect of small doses of botulinum toxin a on neck-shoulder myofascial pain syndrome: a double-blind, randomized, and controlled crossover trial. Clin J Pain. 2006;22(1):90–6. https://doi.org/10.1097/01.ajp.0000151871.51406.c3. PMID: 16340597.
57. Ferrante FM, Bearn L, Rothrock R, King L. Evidence against trigger point injection technique for the treatment of cervicothoracic myofascial pain with botulinum toxin type A. Anesthesiology. 2005;103(2):377–83. https://doi.org/10.1097/00000542-200508000-00021. PMID: 16052120.
58. Wheeler AH, Goolkasian P, Gretz SS. Botulinum toxin A for the treatment of chronic neck pain. Pain. 2001;94(3):255–260. https://doi.org/10.1016/S0304-3959(01)00358-X. PMID: 11731062.
59. Freund BJ, Schwartz M. Treatment of whiplash associated neck pain [corrected] with botulinum toxin-A: a pilot study. J Rheumatol. 2000;27(2):481–4. Erratum in: J Rheumatol 2000 Jun;27(6):1577. PMID: 10685817.
60. Wheeler AH, Goolkasian P, Gretz SS. A randomized, double-blind, prospective pilot study of botulinum toxin injection for refractory, unilateral, cervicothoracic, paraspinal, myofascial pain syndrome. Spine (Phila Pa 1976). 1998;23(15):1662–6; discussion 1667. https://doi.org/10.1097/00007632-199808010-00009. PMID: 9704373.
61. Graboski CL, Gray DS, Burnham RS. Botulinum toxin A versus bupivacaine trigger point injections for the treatment of myofascial pain syndrome: a randomised double blind crossover study. Pain. 2005;118(1-2):170–5. https://doi.org/10.1016/j.pain.2005.08.012. Epub 2005 Oct 3. PMID: 16202527.
62. Kamanli A, Kaya A, Ardicoglu O, Ozgocmen S, Zengin FO, Bayik Y. Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. Rheumatol Int. 2005;25:604–11.
63. DE LA Torre Canales G, Câmara-Souza MB, Poluha RL, Grillo CM, Conti PCR, Sousa MDLR, Rodrigues Garcia RCM, Rizzatti-Barbosa CM. Botulinum toxin type A and acupuncture for masticatory myofascial pain: a randomized clinical trial. J Appl Oral Sci. 2021;29:e20201035. https://doi.org/10.1590/1678-7757-2020-1035. PMID: 34105695; PMCID: PMC8232932.
64. Gerwin R. Botulinum toxin treatment of myofascial pain: a critical review of the literature. Curr Pain Headache Rep. 2012;16(5):413–22. https://doi.org/10.1007/s11916-012-0287-6. PMID: 22777564.
65. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: Transmitter release, spinal activation, and pain behavior. Pain. 2014; [Epub ahead of print]
66. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;358:137–145. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 Jul 1. PMID: 28673722.

67. Tang M, Meng J, Wang J. New engineered-botulinum toxins inhibit the release of pain-related mediators. Int J Mol Sci. 2019;21(1):262. https://doi.org/10.3390/ijms21010262. PMID: 31906003; PMCID: PMC6981458.
68. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107:125–33.
69. Marinelli S, Vacca V, Ricordy R, Uggenti C, Tata AM, Luvisetto S, Pavone F. The analgesic effect on neuropathic pain of retrogradely transported botulinum neurotoxin A involves Schwann cells and astrocytes. PLoS One. 2012;7(10):e47977. https://doi.org/10.1371/journal.pone.0047977. Epub 2012 Oct 24. PMID: 23110146; PMCID: PMC3480491
70. 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(1–3):10–4. https://doi.org/10.1016/j.ejphar.2010.01.020. Epub 2010 Feb 1. PMID: 20123097.
71. Favre-Guilmard C, Auguet M, Chabrier PE. Different antinociceptive effects of botulinum toxin type A in inflammatory and peripheral polyneuropathic rat models. Eur J Pharmacol. 2009;617(1–3):48–53. https://doi.org/10.1016/j.ejphar.2009.06.047. Epub 2009 Jul 1. Erratum in: Eur J Pharmacol. 2010 Feb 25;628(1–3):290. PMID: 19576881.
72. Rosales RL, Arimura K, Takenaga S, Osame M. Extrafusal and intrafusal muscle effects in experimental botulinum toxin-A injection. Muscle Nerve. 1996;19(4):488–96. https://doi.org/10.1002/(SICI)1097-4598(199604)19:4<488::AID-MUS9>3.0.CO;2-8. PMID: 8622728.
73. Lacković Z. New analgesic: focus on botulinum toxin. Toxicon. 2020;179:1–7. https://doi.org/10.1016/j.toxicon.2020.02.008. Epub 2020 Feb 11. PMID: 32174507.
74. Lacković Z. Botulinum toxin and pain. Handb Exp Pharmacol. 2021;263:251–64. https://doi.org/10.1007/164_2019_348. PMID: 32016565
75. Vincent A, Lahr BD, Wolfe F, Clauw DJ, Whipple MO, Oh TH, Barton DL, St Sauver J. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis Care Res (Hoboken). 2013;65(5):786–92. https://doi.org/10.1002/acr.21896. PMID: 23203795; PMCID: PMC3935235.
76. Jones GT, Atzeni F, Beasley M, Flüß E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol. 2015;67(2):568–75. https://doi.org/10.1002/art.38905. PMID: 25323744.
77. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol Suppl. 2005;75:6–21.
78. Häuser W, Walitt B, Fitzcharles MA, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. Arthritis Res Ther. 2014;16:201. [Epub ahead of print]
79. Bhargava J, Hurley JA. Fibromyalgia. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2021 Jul 10. 2021 Jan–. PMID: 31082018.
80. Paulson GW, Gill W. Botulinum toxin is unsatisfactory therapy for fibromyalgia. Mov Disord. 1996;11:459.
81. Asherson RA, Pascoe L. The use of botulinum toxin-A in the treatment of patients with fibromyalgia. J Rheumatol. 2001;28:1740.
82. Montesó-Curto P, García-Martínez M, Gómez-Martínez C, Ferré-Almo S, Panisello-Chavarria ML, Genís SR, Mateu Gil ML, Cubí Guillén MT, Colás LS, Usach TS, Herrero AS, Ferré-Grau C. Effectiveness of three types of interventions in patients with fibromyalgia in a region of Southern Catalonia. Pain Manag Nurs. 2015;16(5):642–52. https://doi.org/10.1016/j.pmn.2015.01.006. Epub 2015 Jun 21. PMID: 26104223.

Chapter 9
Botulinum Toxin Therapy for Pelvic and Urogenital Pain

Introduction

Chronic pelvic pain (CPP) is a disabling disorder which is more common among women.

The American College of Gynecology defines chronic pelvic pain as a noncyclic pain of more than six months duration that localizes to the pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral region, or the buttocks and is of sufficient severity to cause functional disability or require medical care [1]. It affects 5.7–26.5% (both genders) of the population and is more common in women of fertile age [2]. In a prospective study of 5,253 women between the ages of 18 and 50 years, 14.7% met the criteria of chronic (>6 months) pelvic pain and 45% reported reduced work productivity [3]. The cost of female chronic pelvic pain and vulvodynia to the US economy has been estimated to amount 31–72 billion dollars per year [4]. Among men, chronic pelvic pain is the cause of 2 million clinic visits per year [5]. In many affected patients (female or male), CPP is manifested in the form of myofascial pain with trigger points in the muscles of the pelvic floor causing local and referred pain. Pelvic pain can be associated with sexual, musculoskeletal, neurological, and psychological complaints; many affected females complain of dyspareunia (pain during intercourse) and vulvodynia (vulvar pain) [6]. In some patients, chronic pain is a reflection of a serious pathology involving adjacent genitourinary structures. Therefore, a careful examination of the pelvic floor muscles is necessary in every patient with CPP. In suspected patients, anatomical investigation of the pelvic floor and adjacent structures by neuroimaging can disclose the culprit genitourinary pathology.

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_9

Anatomy of the Pelvic Floor

Pelvic floor encompasses three layers of muscles. The most superficial layer consists of bulbocavernosus, ischiocavernosus, superficial transverse perineal, and external anal sphincter. The puborectalis muscle is between superficial and deep muscles. The deepest layer, or pelvic diaphragm, consists of pubococcygeus and ileococcygeus (together they form the levator ani), coccygeus, and ischiococcygeus muscles [7] (Fig. 9.1). Piriformis and obturator internus are also deep muscles. The superficial layers of pelvic floor are innervated by pudendal nerve, while the deepest layer is innervated by S3, S4, and S5 sacral nerve roots.

The referred pain emanating from the trigger points of these muscles can be felt in the distribution and territory of pudendal nerve. The pain emanating from the superficial muscle layer (bulbocavernosus and ischiocavernosus) is referred to the perineum and adjacent urogenital structures. Pain of external anal sphincter may be referred to the posterior pelvic floor. The pain in levator ani and coccygeus muscles would usually radiate to the vagina or sacrococcygeal area. Obturator internus generates referred pain to the anococcygeal region.

Treatment of Chronic Pelvic Pain

A number of therapeutic strategies are employed in the management of chronic pelvic pain. Pelvic floor physical therapy can be helpful and provides some pain relief to 63% of the patients [8]. Pharmacological therapy often encompasses a multimodal approach tailored to the needs of individual patients and may include antispasmodic/anticholinergic drugs, analgesic agents (including nonsteroidal anti-inflammatory drugs), and, in some cases, antibiotics. Amitryptyline and gabapentin are often used to treat pelvic pain. In one investigation, addition of gabapentin to amitriptyline offered better pain relief to pelvic pain patients [9]. Opioid treatment is reserved for recalcitrant pain in the pelvic floor [10].

Alternative therapies such as acupuncture, pollen extract, and mind and body practices have been tried by some with modest results in chronic pelvic pain [11]. Among the three, acupuncture has been studied in more detail and with higher quality studies. In one study [12], patients with pelvic pain due to chronic prostatitis who underwent 20 sessions of acupuncture over 10 weeks demonstrated significant reduction in pelvic pain compared to the group who had sham acupuncture (6-point decrease in NIH-CPSI score at week 10, $P = 0.02$, week 24, $P = 0.04$). In another study [13], investigators compared the effect of electrical acupuncture (EA) with advice and exercise as compared to sham EA with exercise or with exercise only (3 arms) in 63 subjects. After 12 biweekly sessions, symptoms, mostly pain related, improved (6 points in NIH-CPSI) in the group with electrical acupuncture ($P = 0.001$).

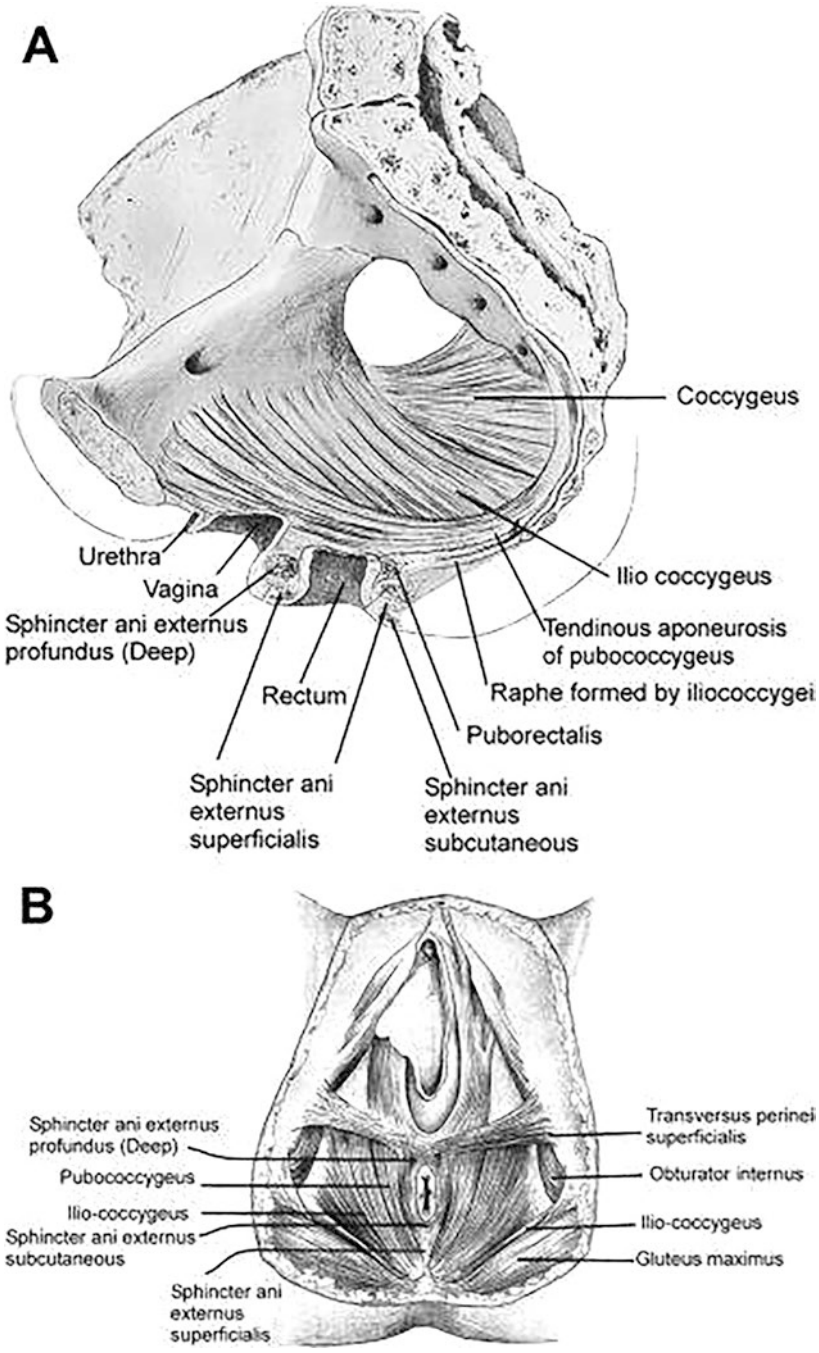

Fig. 9.1 Anatomy of pelvic floor. (From Raizada and Mittal, 2009. *Journal of Gastroentrology Clinic of North America*. Reproduced with permission from the publisher PMC)

Li et al. [14] reviewed the world literature on the effect of acupuncture on pelvic pain caused by prostatitis. Eleven prospective studies with a total of 748 patients were reviewed. Each of the 11 studies came from a single center. The quality of the studies was evaluated by the Cochrane collaboration tool. Five of the 11 studies were blinded and included sham acupuncture. Meta-analysis of the data demonstrated that acupuncture significantly lowered the total NIH-CPSI score, whereas the reduction in NIH-CPSI pain score was modest. Elden et al. [15], however, have found no difference in pain relief between acupuncture and sham acupuncture in 114 pregnant women with a history of chronic pelvic girdle pain. Contradictory results have been reported regarding the effect of acupuncture in primary dysmenorrhea. Some blinded studies have shown significant pain relief with acupuncture compared to sham acupuncture [16], whereas others have reported failure of laser acupuncture to alleviate pain in dysmenorrhea [17].

Pollen extracts containing amino acids, carbohydrates, lipids, vitamins, and minerals have been shown to relax sphincters of the bladder and urethra in addition to having anti-inflammatory effect. A double-blind, placebo-controlled study of 60 patients with CPP [18] revealed lower pain scores and less voiding symptoms in subjects who took pollen extract ($P = 0.05$) at six months after initiation of therapy. In another controlled and blinded study [19] of 139 patients, subjects who took pollen extract demonstrated significantly ($P = 0.008$) lower pain score (subset of NIH-PSI) and showed improved quality of life at 12 weeks ($P = 0.002$). In a recently reported prospective, randomized, controlled study [20], the effect of pollen extract suppository, 1 daily for 10 days, was compared with the ibuprofen 600 mg, 1 tablet in the morning for 10 days in 124 patients. The patients' response was evaluated by patients' reported quality of life outcome (PROs) and NIH-chronic prostatitis symptom index (NIH-CPSI) at three and six months. At the end of evaluation, 88.8% in the pollen group and 27.8% in the ibuprofen group had significant pain relief ($P < 0.0001$). The group that received pollen extract also reported a higher improvement in terms of PROs, when compared with the control group.

Quality studies are not available on mind and body practice approaches for treatment of pelvic pain, which include massage, spinal manipulation, deep-breathing exercises, guided imagery, hypnotherapy, progressive relaxation, qi gong, and tai chi. These practices are based on using the mind to improve physical function.

Neuromodulation techniques (transperineal electromagnetic stimulation, pudendal nerve stimulation, spinal cord stimulation, sacral nerve root stimulation) have been tried and assessed in eight controlled clinical trials [20]. Of these, meta-analysis of the data was only possible for percutaneous tibial nerve stimulation and transcutaneous electrical nerve stimulation. Both techniques offered some degree of pain relief in chronic pelvic pain.

Botulinum Toxin Treatment of Chronic Pelvic Pain

Rational

Botulinum neurotoxin injections into pelvic floor may alleviate pelvic pain via muscular or neural mechanisms. Following intramuscular injection, the toxin travels to neuromuscular junction (via blood or lymphatics) where, through deactivating a SNARE protein (SNAP25 in case of botulinumtoxinA), it blocks the release of acetylcholine from presynaptic vesicles. The result is muscle relaxation and reduced muscle spasm.

On the neural side, injected BoNT influences the sensory nociceptive system and produces analgesia via different mechanisms. It reduces or blocks the function of pain mediators and transmitters (glutamate, substance P, calcitonin gene-related peptide) at the peripheral nerve terminal and at the level of first-order sensory neurons (dorsal root ganglia and trigeminal gangia) [21–26]. Adding botulinum toxins A or B to cultured sensory cells reduces secretion of pain transmitters from these cells [27, 28]. There is now strong evidence that some of the analgesic effects of intramuscularly injected BoNTs emanate from their action at central sensory levels. Sensory neurons of the spinal cord secrete less substance P and demonstrate reduced c-fos activation following intramuscular injection of BoNT-A and B [29, 30]. Both in cell culture and in animal models of pain, peripheral injection of BoNTs reduces the inflammatory response [31, 32].

The analgesic effect of BoNT may be partly related to its central action. Presence of cleaved SNAP-25 in the central neurons after peripheral injection indicates retrograde transfer of the toxin to the central nervous system (CNS) [33]. In CNS, there is also evidence for anterograde propagation of the toxin via the phenomenon of transcytosis [34]. Unilateral, peripherally injected botulinumtoxinA improves bilateral analgesia in animal models of experimental bilateral painful peripheral neuropathy such as those induced by peripheral injection of acidic saline or toxic agents [35, 36].

The toxin can also influence and reduce chronic pain by reducing central sensitization of sensory neurons that occurs in any chronic pain disorder [37]. One mechanism would be by reducing the large non-nociceptive inputs to the spinal cord that in chronic pain conditions can be perceived aberrantly as nociceptive. One such large sensory input comes from intrafusal muscle spindles that report the length of the muscle to the spinal cord neurons. In experimental animals, intramuscular injection of BoNT-A significantly reduces the electrical discharge of the intrafusal nerve fibers (muscle spindles) [38, 39].

Botulinum Neurotoxins Studies in Chronic Pelvic Pain (CPP)

Most studies of BoNT efficacy in chronic pelvic pain are of low quality. The few available high-quality, randomized, blinded, placebo-controlled studies will be reviewed in this chapter, and their findings are summarized.

In 2000, Abbott et al. [40] conducted the first randomized, blinded clinical trial of botulinum toxin therapy in pelvic pain. The study group consisted of 60 patients (30 toxin, 30 placebo) with CPP, 55% of whom had endometriosis and a majority had had surgery to remove foci of endometriosis previously. Patients' major symptoms were nonmenstrual pelvic pain, menstruation-related pelvic pain, dyspareunia, and dysmenorrhea. Patients were injected, under conscious sedation, either with 1cc of study drug (80 units of onabotulinumtoxinA) or a comparable volume of saline into two sites bilaterally within each of puborectalis and pubococcygeus muscles (Fig. 9.1). Participants completed VAS questionnaires for pain, bowel, and bladder questionnaires and had examinations to assess pelvic floor tenderness, vaginal manometry measurements at 2, 4, 8, 12, 16, 20, and 26 weeks after injection. There was significant change from baseline in the botulinum toxin type A group for nonmenstrual pelvic pain assessed by VAS ($P = 0.009$), but not in the placebo group. Both onaA and placebo subjects showed marked improvement of dyspareunia compared to baseline; this improvement was more prominent for onaA ($P = 0.009$ vs. 0.04) group. Both onaA and saline injections decreased the pelvic floor manometric pressure significantly.

In an open label study, the same group of investigators studied the effect of a single injection of 100 units of onabotulinumtoxinA into the pelvic floor (26 women) and multiple injections (2 or more) in 11 women suffering from pelvic pain [41]. The technique of injection was similar to that of their previous report [40]. Second injections were administered no sooner than 26 weeks. Both single and repeat injections reduced nonmenstrual pelvic pain (VAS value of 51 down to 23 $P = 0.04$) and vaginal pressure and dyspareunia (for dyspareunia VAS value of 54 was lowered to 30 for single injection versus 51 down to 23 for multiple injections (P = 0.001).

In another double-blind, placebo-controlled study, the investigators compared the effect of onabotulinumtoxinA (100 units) with saline in 13 male subjects with moderate to severe pelvic pain due to chronic prostatitis [42]. Patients were injected into proximal and mid- bulbospongiosus muscle posterior to the perineal body. The response rate for onaA subjects was 30% compared to 13% for the saline group ($P = 0.002$). The pain component of chronic prostatic symptom index (PCSI) improved significantly in the onaA subjects compared to the placebo group (0.05).

In a double-blind, placebo-controlled study, Falahatkar et al. [43] from the University of Guilan in Iran have investigated the effectiveness of intraurethral BoNT injection into the prostate in 60 adult males with a history of chronic pelvic pain due to chronic prostatitis. Injection results of OnabotulinumtoxinA, 100 or 200 units (depending on prostate volume <30 or >30 CC), diluted in 2cc of normal saline were compared with injection of 2cc of normal saline at one, three, and six

months. The toxin versus saline effect was rated at these timelines by VAS, American Urological Association Symptom Score (AUASS), NIH-CPSI total, and subscale scores and quality of life scores, as well as frequency of diurnal and nocturnal urination. The authors noted a significant decrease in VAS and AUASS among the patients in the toxin group compared to those on placebo from the first month postinjection to the end of the study, as well as significant improvement of quality of life in the patient who received toxin injection. Two patients in the toxin group had mild, transient hematuria.

In another controlled and blinded study of 60 women with pelvic pain, Dessie et al. [44] compared the effect of onaA injection (200 units diluted in 20cc of saline) into the pelvic floor with placebo (saline). The primary outcome was change in participant-reported pain on palpation of the most painful pelvic floor muscle at two weeks. Although more patients in the toxin group met the primary outcome and more patients in the toxin group demonstrated higher "Patient Global Impression of Improvement Index," the difference between toxin and placebo groups was not statistically significant.

In a recent blinded and multicenter study, investigators compared the effect of pelvic floor injection of incobotulinumtoxinA (Xoeomin-Merz) with local anesthetic injection in 80 patients (40 placebo) with chronic pelvic pain [45]. The study group patients carried diverse diagnosis including thoracolumbar junction syndrome (22.5%), idiopathic chronic proctalgia, (21.25%), irritable bowel syndrome (18.75%), provoked vestibulodynia (11.25%), interstitial cystitis (7.5%), and chronic prostatitis (7.5%). Injections were performed under ultrasonography into the tender part of pelvic floor including the pelvic head of obturator internus (OI) and levator ani (LA) muscles. In the toxin group, investigators injected 100 units into OI and 50 units into LA muscles (a total 0f 300 units on both sides). The anesthetic (0.2% ropivocaine hydrochloride) group received 1.5 and 4 cc of anesthetic solution into the levator ani and pelvic head of obturator internus, respectively. The primary outcome measure of the study was a significant change in the 7-point scale of Patient Global Impression-Index (PGI-I) at day 60 after injection. In regard to changes in PGI-I, although more patients at day 60 (post injection) responded to toxin therapy (11 vs. 8), this difference was not statistically significant ($P = 0.43$). Three patients in the botulinum toxin group developed transient incontinence (2 urinary and 1 fecal), which was transient and considered a minor side effect.

Meister et al. [46] have conducted a review and meta-analysis of the published data on the effectiveness of BoNT injections for relief of pelvic pain based on the data published up to the year 2019. Nine studies were included in the final analysis that used a random effects model with robust variance estimation to estimate the pooled mean difference in patient-reported pain scores after botulinum toxin injection. The study found a statistically significant reduction in patient-reported pain scores at six weeks after botulinum toxin injection (mean difference, 20.3; 95% confidence interval, 11.7–28.9) that continued past 12 weeks (mean difference, 19.4; 95% confidence interval, 14.6–24.2). There was also significant improvement in secondary outcomes including dyspareunia and quality of life.

Recently, Karp et al. at NIH reviewed the literature on BoNT therapy in CPP [47]. They noted the safety of toxin injections in the published literature, while emphasizing the need for high-quality studies. The authors described in detail the technique that their group uses at NIH for toxin treatment of CPP. Following a small open label study of 13 patients that produced positive results [48], Dr. Karp's group embarked on a randomized, double-blind, placebo-controlled investigation at NIH (NCT01553201); the results of which will be hopefully available soon.

Comment

Success in BoNT therapy depends highly on using the right injection technique and selection of the right dose. For CPP caused by prostatitis, there is one class A study [43] denoting a B level efficacy (probably effective) [49, 50] when the toxin is injected into the prostate transurethrally. In the case of female CPP, with most studied patients having endometriosis, the class II study of Abbott et al. [40] provides a level C evidence (possibly effective). A number of other studies have shown better response with BoNT-A injection compared to saline or anesthetic injection in pelvic pain [44, 45]; however, the results did not reach statistical significance. These encouraging results clearly show a need for multicenter studies of BoNT efficacy in CPP to determine the right technique and dose for successful CPP treatment.

Other techniques to improve pelvic pain with BoNT are being explored. One such technique involves BoNT blockade of ganglion impar that marks the termination of paravertebral sympathetic chain at the sacroccygeal junction. Blockage of this ganglion with 100 units of onaA (mixed with 5% anesthetic) is reported to ease pelvic pain for six months [51]. Further confirmation of this approach is needed via blinded studies. The current data suggest that in recalcitrant chronic pelvic pain, BoNT treatment can be a useful addition to physical therapy and pharmacological treatment.

Botulinum Toxin Treatment of Dyspareunia and Vaginismus

As mentioned above, dyspareunia (pain during intercourse) can accompany pelvic pain, and botulinum toxin treatment of chronic pelvic pain may also improve the coexisting dyspareunia [44, 45]. Dyspareunia may also occur independent of chronic pelvic pain and in association with different conditions. Park et al. [52] reported the case of a 49–year-old woman with two-year history of fecal dysfunction and dyspareunia who presented with stage II rectal prolapse. She underwent laparoscopic and pelvic floor reconstruction and removal of packets of endometriosis. Four months after a second operation (vaginoplasty), the patient was injected into four sites bilaterally (Fig. 9.2) with 40 units of BoNT-A into levator ani muscles because of continued dyspareunia. Following BoNT injection, patient experienced

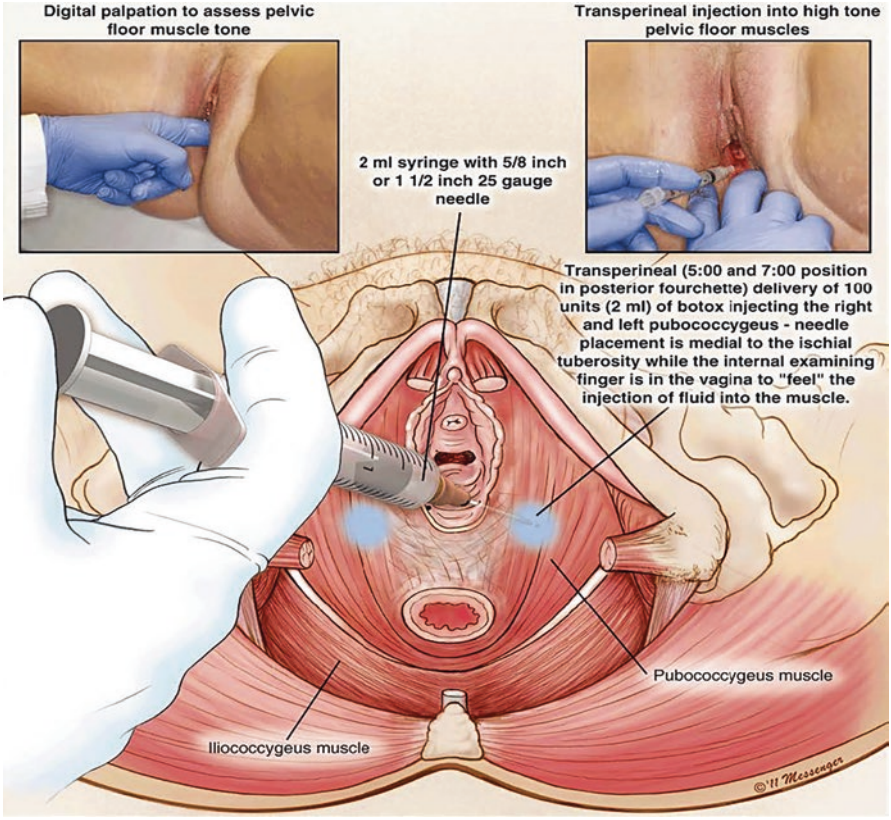

Fig. 9.2 Site of BoNT injection (pubococcygeus muscle), proposed for relief of vulvodynia. (From Goldstien et al., 2011. J Sex Medicine. Printed with permission from John Wiley and Sons)

a significant improvement of dyspareunia and was able to enjoy intercourse for two months.

Vaginismus is involuntary tensing and contraction of the vaginal wall due to any form of vaginal penetration (pelvic examination, tampon, intercourse). It may or may not be associated with dyspareunia. It is a common female disorder that affects one in 200 women [53]. Most cases of vaginismus do not have a defined pathology in the vaginal or pelvic region. Treatment includes physical therapy, sex counseling, psychotherapy add hypnotherapy, as well as the use of oral analgesic and muscle relaxants [54]. Treatment failure is not uncommon.

Brin and Vapnek first reported significant improvement of vaginismus in a 29-year-old woman who noted sensitivity and pain in her vagina after her first intercourse at age 17 [55]. During vaginal examination, there was marked sensitivity of vaginal wall to touch with vigorous pelvic floor contractions. Many treatments over the years including baclofen, paracetamol, amitriptyline, and subtrigonal injection of lidocaine were unsuccessful. Injection of 40 units of onabotulinumtoxinA into

anterior vaginal wall muscles (two sites) resulted in resolution of all symptoms including dyspareunia. Ghazizadeh and Nikzad [56] studied the effect of BoNT injection in 24 women with 3rd and 4th-degree vaginismus who had failed previous nontoxin treatments. Patients received 150–400 units of BoNT-A (Dysport) into puborectalis muscles (3 injections into each side of the vagina). A week post injection, 23 of 24 women showed no or little vaginismus on examination. Eighteen (75%) achieved satisfactory intercourse with 4 experiencing only mild pain. Over a mean of 12.3 months of follow-up, none of the improved patients demonstrated recurrence of vaginismus.

Vulvodynia

Vulvodynia is defined as chronic discomfort and pain in the vulva without objective findings or specific signs of a neurological disorder [57]. The pain is usually burning in character and is often provoked by contact stimulation (sexual activity, tampon contact, etc.). A careful clinical examination and thorough search for pelvic or urogenital pathology are in order before diagnosing a patient with essential (general) vulvodynia. Treatment of volvudynia includes analgesic medications (gabapentin, tricyclic antidepressants), pelvic floor physiotherapy, biofeedback exercises, 5% lidocaine ointment, and acupuncture; all produce only partial relief [58]. Results are often disappointing, and recalcitrant cases are disabling and emotionally drain the patient.

In earlier observations on a single case by Gunter et al. [59] (2004) and another seven patients by Yoon et al. (2007) [60], marked reduction of pain was reported after injection of onaA into vestibule, levator ani, and perineal body in volvudynia. Contrary to these positive observations, Petersen et al. [61] (2009) found no difference between onaA and placebo in respect to pain relief (measured by VAS over 6 months) in a double-blind, placebo-controlled study of 60 subjects with vestibulovulvodynia. OnaA (20 units in 0.5cc saline) or saline (0.5cc) was injected into the bulbospongiosus muscle. Both the placebo and onaA group, however, showed marked decrease in VAS scores compared to baseline ($P < 0.001$). The placebo group also showed marked decrease in sexual stress at six months post injection ($P = 0.04$).

Several subsequent open label clinical trials have suggested efficacy of onaA in reducing pain of vulvodynia. Bertolasi et al. (2009) [62] found that repeated injections of BoNT-A (up to 39 months) in patients with vulvodynia leading to vaginismus improved several patients' symptoms and functions. The authors injected abobotulinumtoxinA (Dysport) into the levator ani bilaterally. When follow-up ended, 63.2% of the patients had completely recovered from vulvodynia and vaginismus. Pelletier et al. (2011) [63] injected 100 units of onaA into vulvar vestibule (50 units on each side) of 20 patients affected with vulvodynia. At three months post injection, both pain (measured by VAS) and quality of life improved significantly compared to baseline values.

The mean VAS score decreased from 8.37 to 1.22 ($P < 0.001$) for 20 patients. The quality and frequency of sexual activity during the first six months after injection also improved ($P < 0.001$). In another open label study [64], the authors described the efficacy of onaA compared to gabapentin in 73 patients with vulvodynia. The onaA dose utilized varied from 40 to 100 units (most patients received >70 units). The mean pre-treatment VAS score was 8.6 (range, 6–10) for the gabapentin treatment group and 8.1 (range, 5–10) for the botulinum toxin A treatment group. Post-treatment VAS scores were significantly reduced for each group (VAS was reduced to 3.2 from 8.6 in the gabapentin group and to 2.5 from 8.1 in the botulinum toxin A group, $P < 0.001$). Authors commented that lack of response in the controlled study of Petersen et al. (2009) could have been due to the low dose of BoNT (20 units of onaA) used in that study. Hansen et al. (2019) [65] followed 79 patients with recalcitrant vulvodynia following incobotulinumtoxin injection into levator ani, pars puborectalis under EMG guidance. The injected dose was 50 units on each side. Patients' pain improved significantly ($P < 0.01$), so did their quality of life ($P < 0.01$) and tenderness to cotton swab test ($P < 0.01$).

Recently, two other blinded studies were reported on BoNT therapy in vulvodynia [66, 67]. In one study that included 44 women in the toxin group and 44 in the placebo (saline) group, both toxin and placebo groups showed significant reduction of pain after injections [66]. Fifty units of BoNT-A were injected at four sites into the lateral and medial bulbocavernosus muscle. Although more patients in the toxin group demonstrated pain relief, the difference between toxin and placebo was not statistically significant. However, during the six months course of the study, significantly more (27% more) patients in the toxin group could participate in vaginal intercourse after toxin injections than the placebo group. No serious adverse effects were noted.

In another randomized and blinded clinical trial [67], investigators compared the effects of 50 and 100 units of onabotulinumtoxinA (Botox-Allergan) with each other and with placebo in 33 women with vulvodynia. Patients received two sets of injections three months apart. Injections were performed into the subcutaneous layers of the dorsal vestibulum. All three groups demonstrated significant reduction of pain after the first injection as assessed by the Von Frey filament test. No significant difference was noted among the three groups. Patients in one of the two toxin groups (100 unit), and those patients in the placebo group, each had a repeat injection with 100 units of toxin after three months. After the second injection, only the placebo group demonstrated significant pain relief as assessed by VAS and Von Frey filament tests ($P = 0.029$ and $P = 0.003$, respectively).

As another site of toxin injection, blocking ganglion of impar can be also considered. Ganglion of impar, the only single ganglion in the nervous system, marks the termination of paravertebral sympathetic chain at the sacroccygeal junction. In patients with pelvic pain, pain relief has been reported with injection of 100 units of onaA into this ganglion [49]. In a recent report [68] on four patients with recalcitrant vulvodynia, repeated injections of 2% lidocaine into this ganglion resulted in almost total disappearance of vulvodynia in two patients and marked reduction of pain in the other two.

Comment

Open label studies cited above uniformly suggest that BoNT therapy is effective and safe in vulvodynia. All blinded studies also show that, compared to placebo or anesthetic, more patients in the toxin group had pain relief, but the values did not reach statistical significance. There are issues with the design and selection of population that could have influenced the results of the blinded studies. In one study [61], the dose was much smaller (20 units of onaA) compared to the 40–100 units used in the open studies. The other blinded studies have shown that placebo was as effective as the toxin in relieving the symptoms of vulvodynia. When the placebo effect is that high, the study cannot properly determine the drug's efficacy for that indication. Therefore, elucidation of true efficacy of BoNT treatment in vulvodynia requires conducting larger studies using sufficient dose of BoNT and, hopefully, in populations that do not demonstrate high placebo effect. A method of injection into pubococcygeus muscle is presented in Fig. 9.2.

Painful Bladder Disorders

A number of bladder disorders have pain as a part of their symptomatology. These include bladder pain syndrome (BPS)/IC, and to a much lesser extent, detrusor muscle overactivity and detrusor sphincter dyssynergia. Since pain is the major symptom of BPS/interstitial cystitis, recent literature has focused on a potential role of BoNTs in relief of pain associated with this syndrome.

Bladder pain syndrome, caused by interstitial cystitis, is defined as a clinical condition characterized by supra-pubic pain (due to bladder filling), diurnal, and nocturnal frequency and urgency in the absence of urinary tract infection or organic urological disease [69]. Cystoscopic evaluation may show presence of glomerulations, petechiae, and sometimes mucosal ulceration. The treatment is often difficult and generally unrewarding. In 2014, Cardella et al. [70] reviewed pharmacological treatments for painful interstitial cystitis. Amitriptyline, gabapentin, duloxetine, and velanfaxine were described as the most commonly used analgesic drugs for this condition with nonsteroidal anti-inflammatory agents (NSAID) and opioids as the second line of treatment. Hydroxizine is used in cases where allergy seems to be a major contributing factor as hydroxyzine inhibits connective tissue mast cell infiltration.

Intravesical drug delivery approach for treatment of IC has gained popularity in recent years. This includes introduction of locally active anesthetics (which have both anti-inflammatory and antimast cell effect), hydraulic acid, and chondroitin sulfate (promote regeneration of damaged urotheliumin BPS) and pentosan polysulfate (approved for oral use by FDA). Pentosan polysulfate has anti-inflammatory effect and degranulates mast cells. These drugs, however, have not shown long-term positive effects.

In a recent review and meta-analysis study [71] of twenty-three randomized clinical trials (RCTs) with 1871 participants, amitriptyline, cyclosporine, and certilozumab all significantly reduced Interstitial Cystitis Symptom Index (ICSI) compared to placebo. The VAS improved significantly in cyclosporine group compared to the group that used pentosan polysulfate sodium. Overall, cyclosporine was found superior to other pharmacologic treatments in efficacy. Rodriquez-Lopez and Mangir recently published an extensive review of nonpharmacological and pharmacological treatments of interstitial cystitis [72]. The nonpharmacological approaches included general relaxation techniques, patient education, behavioral treatments, and physical therapy. Pharmacological approaches were usually multimodal to include oral (amitriptyline, cimetidine, hydroxyzine) and intravesical treatments (heparin, lidocaine, hyaluronic acid, and chondroitin sulfate), as well as hydrodistention and other more invasive treatments. The authors emphasized that most available treatments are not based on a high level of evidence. There is lack of targeted therapies for IC but rather a wealth of empirical approaches with usually inadequate efficacy.

Botulinum Toxin Treatment of BPS/IC

A growing body of information has developed over the past 15 years regarding the role of BoNTs in treatment of bladder pain syndrome (BPS). The literature on this issue includes several open label investigations [73–91] and six double-blind, placebo-controlled clinical trials [92–97]. The open label studies generally suggest efficacy of BoNTs in relieving pain of interstitial cystitis and lack of serious side effects. The six blinded studies will be discussed in some detail below:

In a double-blind, parallel design study, Kuo et al. (2009) [92] compared the efficacy of onabotulinumtoxinA in two groups receiving either 100 or 200 units plus cystoscopic hydrodistention (HD) two weeks later and a third group treated with HD only. All 67 patients in the study had failed to respond to the conventional treatments for BPS. Injections were made into the urothelium of the posterior and lateral bladder walls at 40 sites. In the 200 units group, each injection was 5 units, whereas, the subjects of 100 units group received 2.5 units per injection site. The primary treatment outcome was changed in global response assessment (GRA), a 7-point response from markedly worse to markedly better acknowledged by the patient and assessed at three months post injection. A number of other scales including VAS for pain were also employed. At three months, 80% and 72% of the patients in the 200 unit and 100 unit onaA groups, respectively, had significant improvement expressed in GRA compared to 48% in the HD group (0.032). The VAS pain scores decreased 39%, 55%, and 18% for 100, 200 unit onaA and HD groups, respectively (P = 0.007). The bladder capacity also increased significantly in the onaA groups; 26% in the 100-unit group and 63% in the 200-unit group compared to 4% in the HD group. In the succeeding open arm of the study, GRA score was 71%, 55%, and

30% at 6, 12, and 24 months for the three groups, respectively. The difference between toxin and nontoxin group was statistically significant (P = 0.002).

In another double-blind, placebo-controlled study, Gottsch et al. (2011) [93] compared the effect of onabotulinumtoxinA with saline in 20 women with interstitial cystitis/bladder pain syndrome. Nine patients received the toxin, 50 units into the dome of bladder, periurethrally, one injection in each side. The patients' response was evaluated by symptom evaluation performed using a female modification of the Chronic Prostatitis Symptom Index (CPSI), AUA Symptom Index, Graded Chronic Pain Scale, Perceived Stress Scale, and symptom improvement Visual Analog Scale (VAS). No significant difference was noted between toxin and saline regarding any of the assessed measures. There were no side effects.

In 2014, Manning et al. [94] published the results of their blinded study with use of abobotulinumtoxinA in interstitial cystitis. Twenty-six patients received aboA with hydrodistention, while 27 received saline and hydrodistention. The AboA injections were performed suburothelially. The primary outcome of the study was improvement of total O'Leary –Sant questionnaire score (OLS) but the two components of this test OLS symptom and OLS problem index (OLS-SI, OLS-PI) were also individually assessed. At six weeks and three months post injection, OLS-PI improved significantly more in the aboA with hydrodistention group compared to saline with distension group. However, there was no improvement in OLS-SI or total OLS scores.

In another study (2016) [95], Kuo et al. compared the efficacy of onabotulinum toxinA (injected into urothelium) plus hydrodistention with placebo (saline) in 60 patients (20 received saline) in interstitial cystitis. The study was muticenter, randomized, and double-blinded. The primary endpoint was a decrease in pain assessed using a visual analog scale (VAS) at week 8 after treatment. Secondary endpoints included voiding diary and urodynamic variables. The Wilcoxon sign rank and rank sum tests were used for statistical analyses. At eight weeks post injection, the toxin group demonstrated significantly greater reduction of pain than the saline group ($P = 0.021$). The bladder capacity was also significantly increased in the toxin group. In the toxin group, 63% responded to treatment compared to 15% in the placebo group ($P = 0.028$).

In a two center, blinded study, Chaung and Kuo (2017) [96] looked at the efficacy of lipotoxin (200 abobotulinumtoxinA plus 80 mg of Sphingomyelin) in BPS/IC. Three groups of patients were compared with each other: 1-lipotoxin group (31 patients); 2-onaA group (28 patients); 3-saline group (31 patients). The patients' response was measured by VAS and OLS at four weeks post injection. All three groups improved significantly compared to baseline, a finding that authors contributed to significant placebo effect.

Most recently, Pinto et al. (2018) [97] assessed the efficacy of onabotulinumtoxinA against saline in a double-blind, placebo-controlled trial. Ten patients were injected with 100 units of toxin and 9 patients with the same volume of saline (1cc) into the trigon of the bladder (10 sites). At 12 weeks, pain reduction (measured by VAS) was significant in the toxin group compared to placebo ($P < 0.05$). OnabotulinumtoxinA also significantly improved O'Leary–Sant scores and quality of life scores over placebo at weeks 4, 8, and 12. Important numerical reductions in

voiding frequency were also observed in the toxin group. Urinary tract infections developed in three patients who received onabotulinumtoxinA compared to two patients who received saline.

Injection Technique

For treatment of CBP/IC with botulinumtoxins, investigators have used different techniques of injection. In one communication, just two injections were performed from outside of the bladder paraurethrally [93], whereas all other studies injected through a cystoscope intravesically. The number of intravesical injections varied from 15 to 40 sites in different studies. The total dose of the toxin also differed among different studies. In the case of botulinumtoxinaA (Botox), it varied from 50 to 200 units. Currently, the intravesical injection method is accepted as the preferred method for toxin treatment of CBP/IC (Fig. 9.3).

Although most previous investigators had opted to spare the trigone of the bladder, a recent study suggests that trigone injections can be advantageous in BPS due to the rich sensory innervation of this region [98].

The Proposed Mechanisms of BoNT Action in Bladder Pain

As mentioned earlier in this chapter under pelvic pain, local injection of botulinum toxins can induce analgesic effect by several mechanisms. These include reducing function and release of pain transmitters such as glutamate, calcitonin gene-related peptide (CGRP) and substance P from nerve terminals, DRG and sensory spinal

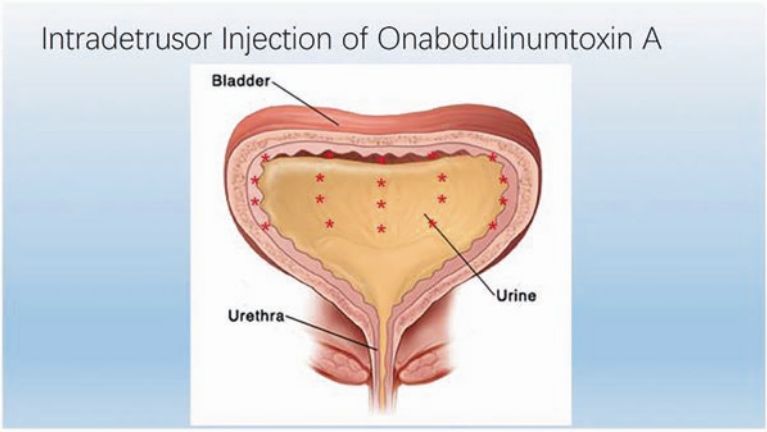

Fig. 9.3 Method of intradetrusor injection into 20 sites (10 units/site) for treatment of CBP/IC. (From Li et al., *Journal of International Medical Research* 2020. Reproduced with permission from the publisher PMC)

neurons, as well as a central effect emanating from the retrograde transfer of the toxin to the central nervous system. Several animal studies support analgesic function of the toxin in bladder pain.

Lucioni et al. (2008) [99] acutely injured bladder explants by bathing them in HCL. The explants demonstrated marked release of calcitonin gene-related peptide (CGRP) and substance P (SP) compared to controls (1235 and 1655 pg/g, respectively; controls, 183 and 449 pg/g, respectively; $P < 0.001$). This increased release of pain mediators was partially inhibited by prior incubation of the explants in a medium that included 10 units of onabotulinumtoxinA (870 and 1033 pg/g; $P < 0.05$ and <0.01). They found cyclophosphamide (CYP) induced chronic inflammation of the bladder significantly increased the release of SP compared to controls (1060 and 605 pg/g, respectively; $P < 0.005$). Again, exposure to onaA partially inhibited the release of SP after CYP-induced cystitis (709 pg/g, $P < 0.05$).

In another study [100], administration of intraperitoneal cyclophosphamide increased the expression of c-fos in L6/S1 segments of the rats' spinal cord (78% and 107%, respectively). This phenomenon was subdued by intravesical instillation of 20 units of onaA prior to cyclophosphamide treatment that resulted in lowering of c-fos level to 50 to 52%. In animals pre-treated with onaA, the intervals between bladder contractions increased by 10 folds. Smith et al. (2005) found that application of cyclophosphamide to bladder urothelium increased ATP release from the inflamed urothelium in 94% of animals [101]. Intravesical infusion of onaA prior to cyclophosphamide therapy reduced the ATP release by 69%.

In another experiment [102], investigators induced severe bladder pain in rats by injecting cyclophosphamide intraperitoneally. Intrathecal infusion of onabotulinumtoxinA at L6 level resulted in marked reduction of the animals' pain behavior.

In 2015, Hanna-Mitchell et al. demonstrated that the bladder urothelium expresses the intracellular targets and the binding protein for cellular uptake of BoNT/A and that the toxin is able to suppress the levels of these targets, as well as hypotonic-evoked ATP release [103]. In a later study [104], Coelho et al. (2016) have shown that in rats' spinal cord injury model, following intratechal injection of onabotulinumtoxinA, painful voiding contractions improved. There was significant reduction of CGRP, a major pain transmitter at sacral dorsal root ganglia and in the spinal cord sensory neurons. Collectively, these observations support the analgesic effects of BoNT-A in animal models of bladder injury-induced pain.

Oliveira et al. (2017) [105] injected onaA and aboA (each 0.5 units diluted in 2cc of normal saline) into the bladder dome of female rats. They found that cleaved SNAP25 in the bladder wall was expressed 1.6 times more after injection of onaA compared to aboA.

Further evidence from animal studies for molecular function of botulinumtoxinA against bladder pain and inflammation was presented in an extensive review of the subject by Yeh et al. (2020) [106].

Comment

Animal studies assessing the efficacy of botulinum neurotoxin injections for bladder pain syndrome/interstitial cystitis (BPS/IC) suggest a variety of mechanisms through which BoNTs can exert an analgesic effect [96–103]. This is supported by a large number of open label studies [75–91]. Among randomized, double-blinded studies, three class II studies have shown superiority of BoNT-A injection combined with hydrodistention in treatment of BPS/IC syndrome compared to hydrodistention or saline alone [92, 94, 95]. Using the efficacy criteria of AAN [49, 50], BoNT-A plus hydrodistention will qualify for a level B (probably effective-minimum two class II studies). Only one blinded study (class II) compared the effect of BoNT-A alone with placebo using the current accepted method of intravesical injections (10 or more sites). This study demonstrated the efficacy of the BoNT-A against placebo [97]. Based on one class II study, current AAN criteria denotes a C level of efficacy (possibly effective).

Studies with long-term follow-ups have shown sustenance of BoNT therapy in treatment of BPS/IC in several open label investigations. Both trigone injections only and trigone sparing injections have been effective [92, 94, 95, 97]. Side effects have been tolerable and the more worrisome ones such as incontinence were more often associated with the use of higher doses of toxins. Overall, the blinded and open studies regarding the use of BoNTs in CBP/IC are encouraging and show a role for toxin therapy for this difficult human pain disorder. There is clearly a need for conducting large, multicenter studies to determine the optimal dose and technique for treatment of CBP/IC with botulinum neurotoxins. A recent study demonstrated that toxin injections can be effective even in the presence of bladder ulcerations and Hunter nodules [107], contradicting the results of a previous observation on this issue [108].

References

1. ACOG practice bulletin; No. 51. March 17, 2004.
2. Ahangari A. Prevalence of chronic pelvic pain among women: an updated review. Pain Physician. 2014;17(2):E141-7. PMID: 24658485.
3. Mathias SD, Kuppermann M, Liberman RF, Lipschutz RC, Steege JF. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. Obstet Gynecol. 1996;87:321–7.
4. Xie Y, Shi L, Xiong X, Wu E, Veasley C, Dade C. Economic burden and quality of life of vulvodynia in the United States. Curr Med Res Opin. 2012;28(4):601–8. https://doi.org/10.1185/03007995.2012.666963. Epub 2012 Mar 20. PMID: 22356119.
5. Duloy AM, Calhoun EA, Clemens JQ. Economic impact of chronic prostatitis. Curr Urol Rep. 2007;8:336–9.
6. Doggweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, Hanno P, Fraser MO, Homma Y, Garrido G, Gomes MJ, Elneil S, van de Merwe JP, Lin ATL, Tomoe H. A standard for terminology in chronic pelvic pain syndromes: A report from the chronic pelvic pain working group of the international continence society. Neurourol Urodyn.

2017;36(4):984–1008. https://doi.org/10.1002/nau.23072. Epub 2016 Aug 26. PMID: 27564065.
7. Raizada V, Mittal RK. Pelvic floor anatomy and applied physiology. Pelvic floor anatomy and applied physiology. Gastroenterol Clin North Am. 2008;37:493–509.
8. Bedaiwy MA, Patterson B, Mahajan S. Prevalence of myofascial chronic pelvic pain and the effectiveness of pelvic floor physical therapy. J Reprod Med. 2013;58(11–12):504–10. PMID: 24568045.
9. Sator-Katzenschlager SM, Scharbert G, Kress HG, Frickey N, Ellend A, Gleiss A, Kozek-Langenecker SA. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. Wien Klin Wochenschr. 2005;117(21–22):761–8. https://doi.org/10.1007/s00508-005-0464-2. PMID: 16416358.
10. Steele A. Opioid use and depression in chronic pelvic pain. Obstet Gynecol Clin North Am. 2014;41(3):491–501. https://doi.org/10.1016/j.ogc.2014.04.005. Epub 2014 Jul 2. PMID: 25155127.
11. Carcini AJ, Pathak R, Young M, Christo PJ. Complementary and alternative treatments for chronic pelvic pain. Curr Pain Headache Rep. 2013;17:316–21.
12. Lee SWH, Liong ML, Yuen KH, et al. Acupuncture vs sham acupuncture for chronic prostatitis/chronic pelvic pain. Am J Med. 2008;21(79):e1–7.
13. Lee SH, Lee BC. Electroacupuncture relieves pain in men with chronic prostatitis/chronic pelvic pain syndrome: three-arm randomized trial. Urology. 2009;73:1036–41.
14. Li J, Dong L, Yan X, Liu X, Li Y, Yu X, Chang D. Is Acupuncture Another Good Choice for Physicians in the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome? Review of the Latest Literature. Pain Res Manag. 2020;2020:5921038. https://doi.org/10.1155/2020/5921038. PMID: 32256909; PMCID: PMC7085851.
15. Elden H, Fagevik-Olsen M, Ostgaard HC, Stener-Victorin E, Hagberg H. Acupuncture as an adjunct to standard treatment for pelvic girdle pain in pregnant women: randomised double-blinded controlled trial comparing acupuncture with non-penetrating sham acupuncture. BJOG. 2008;115(13):1655–68. https://doi.org/10.1111/j.1471-0528.2008.01904.x. Epub 2008 Oct 15. PMID: 18947338.
16. Wade C, Wang L, Zhao WJ, Cardini F, Kronenberg F, Gui SQ, Ying Z, Zhao NQ, Chao MT, Yu J. Acupuncture point injection treatment of primary dysmenorrhoea: a randomised, double blind, controlled study. BMJ Open. 2016;6(1):e008166. https://doi.org/10.1136/bmjopen-2015-008166. PMID: 26733563; PMCID: PMC4716272.
17. Kempf D, Berger D, Ausfeld-Hafter B. Lasernadel-Akupunktur bei Frauen mit Dysmenorrhoe: Eine randomisierte kontrollierte doppelblinde Pilotstudie [Laser needle acupuncture in women with dysmenorrhoea: a randomised controlled double blind pilot trial]. Forsch Komplementmed. 2009;16(1):6–12. German. https://doi.org/10.1159/000193294. Epub 2009 Feb 4. PMID: 19295224.
18. Elist J. Effects of pollen extract preparation Prostat/Poltit on lower urinary tract symptoms in patients with chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized, double-blind, placebo-controlled study. Urology. 2006;67:60–3.
19. Wagenlehner FM, Schneider H, Ludwig M, Schnitker J, Brähler E, Weidner W. A pollen extract (Cernilton) in patients with inflammatory chronic prostatitis-chronic pelvic pain syndrome: a multicenter, randomized, prospective, double-blind, placebo-controlled phase 3 study. Eur Urol. 2009;56:544–51.
20. Cottrell AM, Schneider MP, Goonewardene S, Yuan Y, Baranowski AP, Engeler DS, Borovicka J, Dinis-Oliveira P, Elneil S, Hughes J, Messelink BJ, de C Williams AC. Benefits and harms of electrical neuromodulation for chronic pelvic pain: a systematic review. Eur Urol Focus. 2020;6(3):559–571. https://doi.org/10.1016/j.euf.2019.09.011. Epub 2019 Oct 19. PMID: 31636030.
21. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: Evidence from knockout mice. Neuroscience. 2017;358:137–145. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 Jul 1. PMID: 28673722.

22. Hou YP, Zhang YP, Song YF, Zhu CM, Wang YC, Xie GL. Botulinum toxin type A inhibits rat pyloric myoelectrical activity and substance P release in vivo. Can J Physiol Pharmacol. 2007;85(2):209–14. https://doi.org/10.1139/y07-018. PMID: 17487262.
23. Li C, Micci MA, Murthy KS, Pasricha PJ. Substance P is essential for maintaining gut muscle contractility: a novel role for coneurotransmission revealed by botulinum toxin. Am J Physiol Gastrointest Liver Physiol. 2014;306(10):G839-48. https://doi.org/10.1152/ajpgi.00436.2012. Epub 2014 Apr 3. PMID: 24699329; PMCID: PMC4347745.
24. Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int. 2008;101(3):366–70. https://doi.org/10.1111/j.1464-410X.2007.07312.x. PMID: 18184328.
25. Rapp DE, Turk KW, Bales GT, Cook SP. Botulinum toxin type a inhibits calcitonin gene-related peptide release from isolated rat bladder. J Urol. 2006;175(3 Pt 1):1138–42. https://doi.org/10.1016/S0022-5347(05)00322-8. PMID: 16469640.
26. Bossowska A, Lepiarczyk E, Mazur U, Janikiewicz P, Markiewicz W. Botulinum toxin type A induces changes in the chemical coding of substance P-immunoreactive dorsal root ganglia sensory neurons supplying the porcine urinary bladder. Toxins (Basel). 2015;7(11):4797–816. https://doi.org/10.3390/toxins7114797. PMID: 26580655; PMCID: PMC4663534.
27. Kitamura Y, Matsuka Y, Spigelman I, Ishihara Y, Yamamoto Y, Sonoyama W, Kamioka H, Yamashiro T, Kuboki T, Oguma K. Botulinum toxin type a (150 kDa) decreases exaggerated neurotransmitter release from trigeminal ganglion neurons and relieves neuropathy behaviors induced by infraorbital nerve constriction. Neuroscience. 2009;159(4):1422–9. https://doi.org/10.1016/j.neuroscience.2009.01.066. Epub 2009 Feb 3. Erratum in: Neuroscience. 2009 Jul 7;161(3):950. Kamioka, H [added]; Yamashiro, T [added]. PMID: 19409226.
28. Dolly JO, O'Connell MA. Neurotherapeutics to inhibit exocytosis from sensory neurons for the control of chronic pain. Curr Opin Pharmacol. 2012;12(1):100–8. https://doi.org/10.1016/j.coph.2011.11.001. Epub 2011 Dec 19. PMID: 22188874.
29. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155(4):674–684. https://doi.org/10.1016/j.pain.2013.12.009. Epub 2013 Dec 11. PMID: 24333775; PMCID: PMC3960322.
30. Hong B, Yao L, Ni L, Wang L, Hu X. Antinociceptive effect of botulinum toxin A involves alterations in AMPA receptor expression and glutamate release in spinal dorsal horn neurons. Neuroscience. 2017;357:197–207. https://doi.org/10.1016/j.neuroscience.2017.06.004. Epub 2017 Jun 10. PMID: 28606856.
31. Edvinsson J, Warfvinge K, Edvinsson L. Modulation of inflammatory mediators in the trigeminal ganglion by botulinum neurotoxin type A: an organ culture study. J Headache Pain. 2015;16:555. https://doi.org/10.1186/s10194-015-0555-z. Epub 2015 Aug 6. PMID: 26245187; PMCID: PMC4526514.
32. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107(1-2):125–33. https://doi.org/10.1016/j.pain.2003.10.008. PMID: 14715398.
33. Restani L, Giribaldi F, Manich M, Bercsenyi K, Menendez G, Rossetto O, Caleo M, Schiavo G. Botulinum neurotoxins A and E undergo retrograde axonal transport in primary motor neurons. PLoS Pathog. 2012;8(12):e1003087. https://doi.org/10.1371/journal.ppat.1003087. Epub 2012 Dec 27. PMID: 23300443; PMCID: PMC3531519.
34. Restani L, Antonucci F, Gianfranceschi L, Rossi C, Rossetto O, Caleo M. Evidence for anterograde transport and transcytosis of botulinum neurotoxin A (BoNT/A). J Neurosci. 2011;31(44):15650–9. https://doi.org/10.1523/JNEUROSCI.2618-11.2011. PMID: 22049408; PMCID: PMC6623022.
35. Bach-Rojecky L, Lacković Z. Central origin of the antinociceptive action of botulinum toxin type A. Pharmacol Biochem Behav. 2009;94(2):234–8. https://doi.org/10.1016/j.pbb.2009.08.012. Epub 2009 Sep 2. PMID: 19732788.

36. Lacković Z. Botulinum toxin and pain. Handb Exp Pharmacol. 2021;263:251–64. https://doi.org/10.1007/164_2019_348. PMID: 32016565
37. Aoki KR, Francis J. Updates on the antinociceptive mechanism hypothesis of botulinum toxinA. Parkinsonism Relat Disord. 2011;17(Suppl 1):S28–33.
38. Phadke CP, On AY, Ismail F, Boulias C. Botulinum toxin induces chemodenervation of intrafusal and extrafusal fibers. J Child Neurol. 2013;28(6):819. https://doi.org/10.1177/0883073813487025. PMID: 23677547.
39. Rosales RL, Arimura K, Takenaga S, Osame M. Extrafusal and intrafusal muscle effects in experimental botulinum toxin-A injection. Muscle Nerve. 1996;19(4):488–96. https://doi.org/10.1002/(SICI)1097-4598(199604)19:4<488::AID-MUS9>3.0.CO;2-8. PMID: 8622728.
40. 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(4):915–23. https://doi.org/10.1097/01.AOG.0000237100.29870.cc. PMID: 17012454.
41. Nesbitt-Hawes EM, Won H, Jarvis SK, Lyons SD, Vancaillie TG, Abbott JA. Improvementin pelvic pain with botulinum toxin type A – Single vs. repeat injections. Toxicon. 2013;63:83–7.
42. 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(1):72-6. https://doi.org/10.3109/00365599.2010.529820. Epub 2010 Nov 9. PMID: 21062115.
43. 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(4):641–9. https://doi.org/10.1111/bju.12951. Epub 2015 May 25. PMID: 25307409.
44. Dessie SG, Von Bargen E, Hacker MR, Haviland MJ, Elkadry E. A randomized, double-blind, placebo-controlled trial of onabotulinumtoxin A trigger point injections for myofascial pelvic pain. Am J Obstet Gynecol. 2019;221(5):517.e1–517.e9. https://doi.org/10.1016/j.ajog.2019.06.044. Epub 2019 Jun 27. PMID: 31254522.
45. Levesque A, Ploteau S, Michel F, Siproudhis L, Bautrant E, Eggermont J, Rabischong B, Volteau C, Perrouin-Verbe MA, Labat JJ. Botulinum toxin infiltrations versus local anaesthetic infiltrations in pelvic floor myofascial pain: Multicentre, randomized, double-blind study. Ann Phys Rehabil Med. 2021;64(1):101354. https://doi.org/10.1016/j.rehab.2019.12.009. Epub 2020 Jan 22. PMID: 31981833.
46. Meister MR, Brubaker A, Sutcliffe S, Lowder JL. Effectiveness of Botulinum Toxin for Treatment of Symptomatic Pelvic Floor Myofascial Pain in Women: A Systematic Review and Meta-analysis. Female Pelvic Med Reconstr Surg. 2021;27(1): e152–e160. https://doi.org/10.1097/SPV.0000000000000870. PMID: 32301801; PMCID: PMC7793632.
47. Karp BI, Tandon H, Vigil D, Stratton P. Methodological approaches to botulinum toxin for the treatment of chronic pelvic pain, vaginismus, and vulvar pain disorders. Int Urogynecol J. 2019;30(7):1071–1081. https://doi.org/10.1007/s00192-018-3831-z. Epub 2019 Jan 7. PMID: 30617506.
48. Tandon HK, Stratton P, Sinaii N, Shah J, Karp BI. Botulinum toxin for chronic pelvic pain in women with endometriosis: a cohort study of a pain-focused treatment. Reg Anesth Pain Med. 2019:rapm-2019-100529. https://doi.org/10.1136/rapm-2019-100529. Epub ahead of print. PMID: 31289238; PMCID: PMC6946887.
49. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology. 2008;71(20):1639–43. https://doi.org/10.1212/01.wnl.0000336535.27773.c0. PMID: 19001255.
50. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008 Nov 11;71(20):1634–1638. https://doi.org/10.1212/01.wnl.0000336533.19610.1b. PMID: 19001254.

51. Lim SJ, Park HJ, Lee SH, Moon DE. Ganglion impar block with botulinum toxin type a for chronic perineal pain – a case report. Korean J Pain. 2010;23:65–9.
52. Park AJ, Paraiso MFR. Successful use of botulinum toxin type a in the treatment of refractory postoperative dyspareunia. Obstet Gynecol. 2009;114(2 Pt 2):484–7. https://doi.org/10.1097/AOG.0b013e3181998ce1. PMID: 19622971
53. Barnes J. Primary vaginismus (Part 1): Social and clinical features. Ir Med J. 1986;79(3):59–62. PMID: 3700068
54. Pacik PT. Understanding and treating vaginismus: a multimodal approach. Int Urogynecol J. 2014;25(12):1613–20. https://doi.org/10.1007/s00192-014-2421-y. Epub 2014 Jun 4. PMID: 24894201
55. Brin MF, Vapnek JM. Treatment of vaginismus with botulinum toxin injections. Lancet. 1997 Jan 25;349(9047):252–3. https://doi.org/10.1016/S0140-6736(05)64862-3. Erratum in: Lancet 1997 Mar 1;349(9052):656. PMID: 9014917.
56. Ghazizadeh S, Nikzad M. Botulinum toxin in the treatment of refractory vaginismus. Obstet Gynecol. 2004 Nov;104(5 Pt 1):922–5. https://doi.org/10.1097/01.AOG.0000141441.41178.6b. PMID: 15516379.
57. Moyal-Barracco M, Lynch PJ. 2003 ISSVD terminology and classification of vulvodynia: A historical perspective. J Reprod Med. 2004;49:772–7.
58. Lotery HE, McClure N, Galask RP. Vulvodynia. Lancet. 2004;363:1058–60.
59. Gunter J, Brewer A, Tawfik O. Botulinum toxin a for vulvodynia: a case report. J Pain. 2004;5(4):238–40. https://doi.org/10.1016/j.jpain.2004.02.575. PMID: 15162347
60. Yoon H, Chung WS, Shim BS. Botulinum toxin A for the management of vulvodynia. Int J Impot Res. 2007 Jan–Feb;19(1):84–87. https://doi.org/10.1038/sj.ijir.3901487. Epub 2006 May 18. PMID: 16728964.
61. Petersen CD, Giraldi A, Lundvall L, Kristensen E. Botulinum toxin type A – a novel treatment for provoked vestibulodynia? Results from a randomized, placebo controlled, double blinded study. J Sex Med. 2009;6:2523–37.
62. Bertolasi L, Frasson E, Cappelletti JY, Vicentini S, Bordignon M, Graziottin A. Botulinum neurotoxin type A injections for vaginismus secondary to vulvar vestibulitis syndrome. Obstet Gynecol. 2009;114(5):1008–16. https://doi.org/10.1097/AOG.0b013e3181bb0dbb. PMID: 20168100
63. Pelletier F, Parratte B, Penz S, Moreno JP, Aubin F, Humbert P. Efficacy of high doses of botulinum toxin A for treating provoked vestibulodynia. Br J Dermatol. 2011 Mar;164(3):617–22. https://doi.org/10.1111/j.1365-2133.2011.10235.x. PMID: 21275944.
64. Jeon Y, Kim Y, Shim B, Yoon H, Park Y, Shim B, Jeong W, Lee D. A retrospective study of the management of vulvodynia. Korean J Urol. 2013 Jan;54(1):48–52. https://doi.org/10.4111/kju.2013.54.1.48. Epub 2013 Jan 18. PMID: 23362448; PMCID: PMC3556554.
65. Hedebo Hansen T, Guldberg R, Meinert M. Botulinum toxin-treatment of localized provoked vulvodynia refractory to conventional treatment. Eur J Obstet Gynecol Reprod Biol. 2019 Mar;234:6–9. https://doi.org/10.1016/j.ejogrb.2018.12.013. Epub 2018 Dec 15. PMID: 30639955.
66. Haraldson P, Mühlrad H, Heddini U, Nilsson K, Bohm-Starke N. Botulinum toxin A as a treatment for provoked vestibulodynia: a randomized controlled trial. Obstet Gynecol. 2020 Sep;136(3):524–532. https://doi.org/10.1097/AOG.0000000000004008. PMID: 32769643.
67. Diomande I, Gabriel N, Kashiwagi M, Ghisu GP, Welter J, Fink D, Fehr MK, Betschart C. Subcutaneous botulinum toxin type A injections for provoked vestibulodynia: a randomized placebo-controlled trial and exploratory subanalysis. Arch Gynecol Obstet. 2019 Apr;299(4):993–1000. https://doi.org/10.1007/s00404-019-05043-w. Epub 2019 Feb 1. PMID: 30707361.
68. Hong DG, Hwang SM, Park JM. Efficacy of ganglion impar block on vulvodynia: Case series and results of mid- and long-term follow-up. Medicine (Baltimore). 2021 Jul 30;100(30):e26799. https://doi.org/10.1097/MD.0000000000026799. PMID: 34397737; PMCID: PMC8322564.

69. Van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, Elneil S, Fall M, Hohlbrugger G, Irwin P, Mortensen S, van Ophoven A, Osborne JL, Peeker R, Richter B, Riedl C, Sairanen J, Tinzl M, Wyndaele JJ. Diagnostic criteria, classification, and for painful bladder syndrome interstitial cystitis: an ESSIC proposal. Eur Urol. 2008;53:60–7.
70. Gardella B, Porru D, Allegri M, Bogliolo S, Iacobone AD, Minella C, Nappi RE, Ferrero S, Spinillo A. Pharmacokinetic considerations for therapies used to treat interstitial cystitis. Expert Opin Drug Metab Toxicol. 2014 May;10(5):673–84. https://doi.org/10.1517/17425255.2014.896338. Epub 2014 Mar 12. PMID: 24621003.
71. Di XP, Luo DY, Jin X, Zhao WY, Li H, Wang KJ. Efficacy and safety comparison of pharmacotherapies for interstitial cystitis and bladder pain syndrome: a systematic review and Bayesian network meta-analysis. Int Urogynecol J. 2021 May;32(5):1129–1141. https://doi.org/10.1007/s00192-020-04659-w. Epub 2021 Feb 27. PMID: 33638677.
72. Lopez SR, Mangır N. Current standard of care in treatment of bladder pain syndrome/interstitial cystitis. Ther Adv Urol. 2021 Jun 12;13:17562872211022478. https://doi.org/10.1177/17562872211022478. PMID: 34178118; PMCID: PMC8202321.
73. Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. Urology. 2004;64:871–5.
74. Giannantoni A, Mearini E, Del Zingaro M, Proietti S, Porena M. Two-year efficacy and safety of botulinum a toxin intravesical injections in patients affected by refractory painful bladder syndrome. Curr Drug Deliv. 2010;7:1–4.
75. Giannantoni A, Costantini E, Di Stasi SM, Tascini MC, Bini V, Porena M. Botulinum A toxin intravesical injections in the treatment of painful bladder syndrome: a pilot study. Eur Urol. 2006;49:704–9.
76. Pinto R, Lopes T, Frias B, Silva JA, Silva CM, Cruz C, Cruz F, Dinis P. Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. Eur Urol. 2010;58:360–5.
77. Pinto R, Lopes T, Silva J, Silva JA, Silva CM, Cruz C, Cruz F, Dinis P. Persistent therapeutic effect of repeated injections of onabotulinum toxin A in refractory bladder pain syndrome/interstitial cystitis. J Urol. 2013;189:548–53.
78. Giannantoni A, Cagini R, Del Zingaro M, et al. Botulinum A toxin intravesical injections for painful bladder syndrome: impact upon pain, psychological functioning and Quality of Life. Curr Drug Deliv. 2010;7:442–6.
79. Shie JH, Liu HT, Wang YS, KuoHC. Immunohistochemical evidence suggests repeated intravesical application of botulinum toxin A injections may improve treatment efficacy of interstitial cystitis/bladder pain syndrome. BJU Int. 2013;111:638–46.
80. Ramsay AK, Small DR, Conn IG. Intravesical botulinum toxin type A in chronic interstitial cystitis: results of a pilot study. Surgeon. 2007;5:331–3.
81. Lee CL, Kuo HC. Intravesical botulinum toxin A injections do not benefit patients with ulcer type interstitial cystitis. Pain Phys. 2013;16:109–16.
82. Chung SD, Kuo YC, Kuo HC. Intravesical onabotulinumtoxinA injections for refractory painful bladder syndrome. Pain Phys. 2012;15:197–202.
83. Kuo HC. Repeated intravesical onabotulinumtoxinA injections are effective in treatment of refractory interstitial cystitis/bladder pain syndrome. Int J Clin Pract. 2013 May;67(5):427–434. https://doi.org/10.1111/ijcp.12113. PMID: 23574103.
84. Gao Y, Liao L. Intravesical injection of botulinum toxin A for treatment of interstitial cystitis/bladder pain syndrome: 10 years of experience at a single center in China. Int Urogynecol J. 2015 Jul;26(7):1021–6. https://doi.org/10.1007/s00192-015-2631-y. Epub 2015 Feb 18. PMID: 25690160.
85. Akiyama Y, Nomiya A, Niimi A, Yamada Y, Fujimura T, Nakagawa T, Fukuhara H, Kume H, Igawa Y, Homma Y. Botulinum toxin type A injection for refractory interstitial cystitis: A randomized comparative study and predictors of treatment response. Int J Urol. 2015 Sep;22(9):835–841. https://doi.org/10.1111/iju.12833. Epub 2015 Jun 2. PMID: 26041274.

86. Lee CL, Kuo HC. Long-Term Efficacy and Safety of Repeated Intravescial OnabotulinumtoxinA Injections Plus Hydrodistention in the Treatment of Interstitial Cystitis/Bladder Pain Syndrome. Toxins (Basel). 2015 Oct 22;7(10):4283–4293. https://doi.org/10.3390/toxins7104283. PMID: 26506388; PMCID: PMC4626734.
87. Zeng J, Lai H, Zheng D, Zhong L, Huang Z, Wang S, Zou W, Wei L. Effective treatment of ketamine-associated cystitis with botulinum toxin type a injection combined with bladder hydrodistention. J Int Med Res. 2017;45(2):792–7. https://doi.org/10.1177/0300060517693956. Epub 2017 Mar 8. PMID: 28415952; PMCID: PMC5536663
88. Zeng J, Lai H, Zheng D, Zhong L, Huang Z, Wang S, Zou W, Wei L. Effective treatment of ketamine-associated cystitis with botulinum toxin type a injection combined with bladder hydrodistention. J Int Med Res. 2017 Apr;45(2):792–97. https://doi.org/10.1177/0300060517693956. Epub 2017 Mar 8. PMID: 28415952; PMCID: PMC5536663.
89. Rappaport YH, Zisman A, Jeshurun-Gutshtat M, Gerassi T, Hakim G, Vinshtok Y, Stav K. Safety and feasibility of intravesical instillation of botulinum toxin-A in hydrogel-based slow-release delivery system in patients with interstitial cystitis-bladder pain syndrome: a pilot study. Urology. 2018 Apr;114:60–65. https://doi.org/10.1016/j.urology.2017.12.028. Epub 2018 Jan 4. PMID: 29307733.
90. Mateu Arrom L, Gutierrez Ruiz C, Palou J, Errando-Smet C. Onabotulinumtoxin a injection with or without hydrodistension for treatment of bladder pain syndrome. Int Urogynecol J. 2021 May;32(5):1213–1219. https://doi.org/10.1007/s00192-020-04451-w. Epub 2020 Jul 28. PMID: 32725367.
91. Li B, Leng Q, Li C, Tan X, Su W, Li C. Comparison of intravesical instillation of hyaluronic acid with intradetrusor botulinum toxin A injection or cystoscopic hydrodistention for ketamine-associated cystitis. J Int Med Res. 2020 Nov;48(11):300060520973100. https://doi.org/10.1177/0300060520973100. PMID: 33259240; PMCID: PMC7711230.
92. Kuo HC, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int. 2009 Sep;104(5):657–661. https://doi.org/10.1111/j.1464-410X.2009.08495.x. Epub 2009 Mar 30. PMID: 19338543.
93. Gottsch HP, Miller JL, Yang CC, Berger RE. A pilot study of botulinum toxin for interstitial cystitis/painful bladder syndrome. Neurourol Urodyn. 2011 Jan;30(1):93–96. https://doi.org/10.1002/nau.20946. Epub 2010 Jun 29. PMID: 20589903.
94. Manning J, Dwyer P, Rosamilia A, Colyvas K, Murray C, Fitzgerald E. A multicentre, prospective, randomised, double-blind study to measure the treatment effectiveness of abobotulinum A (AboBTXA) among women with refractory interstitial cystitis/bladder pain syndrome. Int Urogynecol J. 2014 May;25(5):593–599. https://doi.org/10.1007/s00192-013-2267-8. Epub 2013 Nov 26. PMID: 24276074.
95. Kuo HC, Jiang YH, Tsai YC, Kuo YC. Intravesical botulinum toxin-A injections reduce bladder pain of interstitial cystitis/bladder pain syndrome refractory to conventional treatment – A prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial. Neurourol Urodyn. 2016 Jun;35(5):609–614. https://doi.org/10.1002/nau.22760. Epub 2015 Apr 24. PMID: 25914337.
96. Chuang YC, Kuo HC. A prospective, multicenter, double-blind, randomized trial of bladder instillation of liposome formulation onabotulinumtoxina for interstitial cystitis/bladder pain syndrome. J Urol. 2017 Aug;198(2):376–382. https://doi.org/10.1016/j.juro.2017.02.021. Epub 2017 Feb 12. PMID: 28202358.
97. Pinto RA, Costa D, Morgado A, Pereira P, Charrua A, Silva J, Cruz F. Intratrigonal onabotulinumtoxinA improves bladder symptoms and quality of life in patients with bladder pain syndrome/interstitial cystitis: a pilot, single center, randomized, double-blind, Placebo Controlled Trial. J Urol. 2018 Apr;199(4):998–1003. https://doi.org/10.1016/j.juro.2017.10.018. Epub 2017 Oct 13. PMID: 29031769.

98. Dobberfuhl AD, van Uem S, Versi E. Trigone as a diagnostic and therapeutic target for bladder-centric interstitial cystitis/bladder pain syndrome. Int Urogynecol J. 2021 Jun 22. https://doi.org/10.1007/s00192-021-04878-9. Epub ahead of print. PMID: 34156506.
99. Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int. 2008;101:366–70.
100. Vemulakonda VM, Somogyi GT, Kiss S, Salas NA, Boone TB, Smith CP. Inhibitory effect of intravesically applied botulinum toxin A in chronic bladder inflammation. J Urol. 2005;173:621–4.
101. Smith CP, Vemulakonda VM, Kiss S, Boone TB, Somogyi GT. Enhanced ATP release from rat bladder urothelium during chronic bladder inflammation: effect of botulinum toxin A. Neurochem Int. 2005 Sep;47(4):291–7. https://doi.org/10.1016/j.neuint.2005.04.021. PMID: 15970360.
102. Coelho A, Oliveira R, Rossetto O, Cruz CD, Cruz F, Avelino A. Intrathecal administration of botulinum toxin type A improves urinary bladder function and reduces pain in rats with cystitis. Eur J Pain. 2014 Nov;18(10):1480–9. https://doi.org/10.1002/ejp.513. Epub 2014 Apr 23. PMID: 24756904.
103. Hanna-Mitchell AT, Wolf-Johnston AS, Barrick SR, Kanai AJ, Chancellor MB, de Groat WC, Birder LA. Effect of botulinum toxin A on urothelial-release of ATP and expression of SNARE targets within the urothelium. Neurourol Urodyn. 2015 Jan;34(1):79–84. https://doi.org/10.1002/nau.22508. Epub 2013 Oct 26. PMID: 24167028; PMCID: PMC4035459.
104. Coelho A, Oliveira R, Cruz F, Cruz CD. Impairment of sensory afferents by intrathecal administration of botulinum toxin A improves neurogenic detrusor overactivity in chronic spinal cord injured rats. Exp Neurol. 2016 Nov;285(Pt B):159–166. https://doi.org/10.1016/j.expneurol.2016.05.029. Epub 2016 May 25. PMID: 27235935.
105. Oliveira R, Coelho A, Charrua A, Avelino A, Cruz F. Expression of cleaved SNAP-25 after bladder wall injection of onabotulinumtoxina or abobotulinumtoxina: A comparative study in the mice. Neurourol Urodyn. 2017 Jan;36(1):86–90. https://doi.org/10.1002/nau.22900. Epub 2015 Oct 16. PMID: 26472491.
106. Yeh TC, Chen PC, Su YR, Kuo HC. Effect of botulinum toxin A on bladder pain-molecular evidence and animal studies. Toxins (Basel). 2020 Feb 3;12(2):98. https://doi.org/10.3390/toxins12020098. PMID: 32028597; PMCID: PMC7076962.
107. Pinto R, Lopes T, Costa D, Barros S, Silva J, Silva C, Cruz C, Dinis P, Cruz F. Ulcerative and nonulcerative forms of bladder pain syndrome/interstitial cystitis do not differ in symptom intensity or response to onabotulinum toxin A. Urology. 2014 May;83(5):1030–4. https://doi.org/10.1016/j.urology.2014.01.018. PMID: 24767520.
108. Lee CL, Kuo HC. Intravesical botulinum toxin a injections do not benefit patients with ulcer type interstitial cystitis. Pain Physician. 2013 Mar–Apr;16(2):109–16. PMID: 23511677.

Chapter 10
Botulinum Toxin Treatment of Chronic Facial Pain: Trigeminal Neuralgia and Temporo-Mandibular Disorders

Trigeminal Neuralgia (TN)

Trigeminal neuralgia (TN) is one of the most severe forms of human pain and a cause of significant distress and depression in afflicted patients. In the United States, the estimated incidence of TN is 4/100,000 individuals [1]. Trigeminal neuralgia is more common after the age of 50 with the peak onset of symptoms between ages 53 and 57 years [2]. Women are more frequently affected than men with the ratio of 3 to 2 [3]. The pain is almost always unilateral, more often affecting the right side of the face (60%) [4].

Etiologically, three types of trigeminal neuralgia are recognized: classic, secondary, and idiopathic. The classic form includes majority of cases (over 80%). It is caused by compression of the trigeminal nerve by an anomalous vessel, usually the superior cerebellar artery, but vertebral artery or anterior inferior cerebellar arteries can be culprits as well. In most cases, the neurovascular compression can be visualized by magnetic resonance imaging. The secondary form of TN can be seen in patients suffering from multiple sclerosis, in association with space-occupying lesions and following craniofacial trauma. In approximately 10% of patients with TN, no cause can be found (idiopathic TN).

The pain of TN is severe, often described as jabbing, stabbing, and shock-like pain. It involves one side of the face and may affect any branch of the trigeminal nerve, but maxillary (V2) and mandibular branch (V3) involvement is more common. Isolated V1 branch (ophthalmic) involvement is rare (5%) and, when present, is usually accompanied by mild autonomic symptoms (lacrimation, rhinorrhea, conjunctival injection) [5]. The pain of TN usually lasts seconds, but in some cases, pain may last up to two minutes. Bouts of pain may occur multiple times a day and disable the patient. Facial movements, eating, speaking, chewing, and shaving often exacerbate the pain. Many patients have local trigger points in the face that upon

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_10

touching provoke severe pain. In the chronic state, a high proportion of the patients live in constant fear and anticipation of upcoming bouts of pain.

In the international classification of headache disorders, edition 3 (ICHD-3), four diagnostic criterion are required for diagnosis of trigeminal neuralgia [5]:

1. Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, also fulfilling criteria 2 and 3
2. Pain has all the following characteristics: (a) lasting from fraction of a second to two minutes; (b) severe intensity; (c) electric shock-like shooting, stabbing, or sharp quality
3. Precipitated by innocuous stimuli within the affected trigeminal distribution
4. Not better accounted for by another ICHD-3 diagnosis

Treatment

Pharmacologic Treatment

Pharmacologic treatment of trigeminal neuralgia includes preventive and abortive treatments. Since TN is a form of neuropathic pain, the drugs that are most effective in TN are those that are used commonly for other forms of neuropathic pain. Carbamazepine (200–1200 mg) and oxcarbazepine (600–1800 mg) are now considered the first-line drugs for treatment of TN [6]. Treatment needs to start with lower dose and increase slowly to build tolerance (especially among women). Up to 90% of the patients with TN initially respond to carbamazepine and oxcarbazepine, but the effects wane over time. Approximately 40% of the patients discontinue treatment due to side effects such as nausea, dizziness, and double vision. Other drugs used for preventive treatment of pain attacks in TN include lamotrigine, gabapentin, phenytoin, topiramate, pregabalin, valproic acid, and clonazepam. Baclofen, a muscle relaxant and selective GABA-B receptor agonist, also may work using a dose of 30–80 mg/day. In one blinded study, combination of carbamazepine and baclofen proved more effective, than either of the two alone [7].

Abortive treatment of acute pain attacks in TN includes using local application of lidocaine patch and, in more severe cases, intravenous infusion of magnesium and lidocaine [8, 9]. Medical treatment of trigeminal neuralgia has been described in detail in several recent reviews [10–13].

Surgical Treatment

In many cases, trigeminal neuralgia is caused by an anomalous artery or vein impinging against the trigeminal nerve at or close to its exit point from the brain stem. This compression causes focal demyelination in the nerve which, over time,

leads to generation of ectopic discharges. Hence, in recalcitrant cases of trigeminal neuralgia with demonstrable MRI abnormalities, neurovascular decompression can be helpful. Surgical procedures for treatment of TN include the following approaches:

1. Microvascular decompression is a widely used procedure for management of pain attacks in TN and can provide pain relief up to 10 years or longer. It is considered the most effective procedure. Side effects include loss of hearing, cerebrospinal fluid (CSF) leaks, infarction, and cerebellar hematoma [11].
2. Ablative surgery includes rhizotomy, mechanical balloon compression, thermocoagulation, and chemical injections. They can cause sensory deficit in the distribution of trigeminal nerve and anesthesia dolorosa.
3. Radiosurgery including Gamma knife delivers ionizing radiation to trigeminal nerve root. It may cause facial sensory loss and paresthesias.
4. Peripheral neurectomy and nerve block

Anatomy and Physiology of Trigeminal Sensory System

Sensations from the face, gums, inner part of the cheeks, and teeth are conveyed to the central nervous system via three branches of the trigeminal nerve, namely, the ophthalmic, maxillary, and mandibular [14]. The ophthalmic branch innervates the skin of the forehead and top of the head and provides corneal sensation. The ophthalmic sensory branch to cornea is the afferent arm of corneal reflex, one of the most informative reflexes used in clinical medicine. The ophthalmic branch enters the cranium through the superior orbital fissure, travels with the maxillary branch in the cavernous sinus and then, along with maxillary and mandibular branches, converges into the trigeminal ganglion (Gasserian ganglion) located in the middle fossa.

The maxillary branch of the trigeminal nerve innervates the middle part of the face, cheek, upper teeth and mucosa of the nasal cavity, soft and hard palates, and the pharynx (Fig. 10.1). Innervation of the nasal mucosa is the basis for sternutatory reflex (unilateral grimacing after gently putting a Q-tip inside one nostril) that tests the integrity of the V1 branch of the trigeminal nerve. The maxillary nerve leaves the face through the inferior orbital fissure and enters the skull via foramen rotundum.

The sensory part of the mandibular nerve (3rd division of trigeminal nerve) carries information from the skin of the lower face, side of the face and head, lower teeth, anterior two-thirds of the tongue, and mucosa of the mouth and cheeks. The mandibular nerve enters the skull via foramen ovale and ends in the inferior part of the trigeminal ganglion.

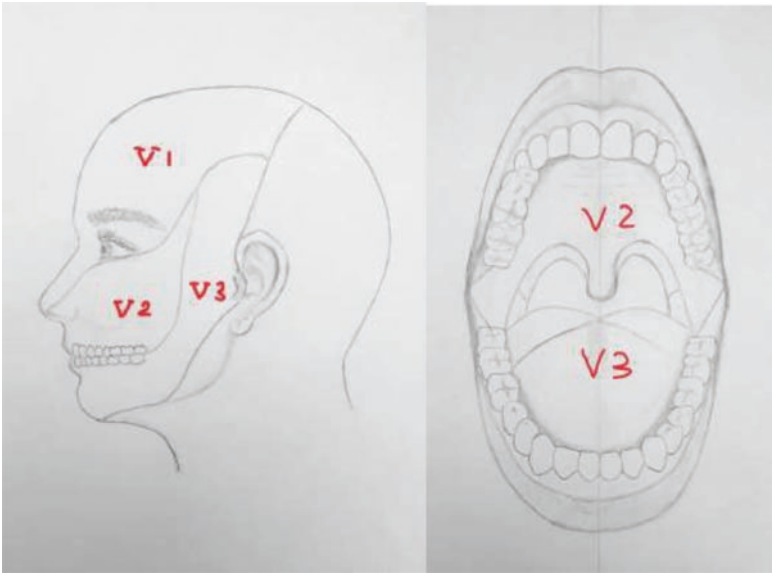

Fig. 10.1 Sensory distribution of first (ophthalmic), second (maxillary), and third (mandibular) divisions of the trigeminal nerve. (Drawings, courtesy of Shahroo Etemad-Moghadam DDS, MS)

Botulinum Toxin Treatment of Trigeminal Neuralgia

Over the past two decades, animal and laboratory studies have demonstrated the effect of BoNTs upon trigeminal nerve and neurons and in relieving pain behavior in animal models of trigeminal pain. Several major pain mediators, specific pain receptors, and pain-activating voltage--gated sodium channels are highly expressed in the neurons of trigeminal ganglia and trigeminal nerve endings.

Cultured trigeminal neurons, within days, release large amounts of calcitonin gene-related peptide (CGRP), a major inflammatory pain mediator [15]. Transient receptor potential vanilloid 1 (TRPV1), a cation channel, is recognized as a major contributor to nociception since its activation releases CGRP. TRPV1 is highly expressed in a large number ($\geq$90%) of trigeminal neurons. Exposure of rats' cultured trigeminal neurons to retargeted BoNT-A with nociceptive potential directly reduces the release of CGRP from these cells [16]. Subcutaneous injection of 0.25 and 0.5 ng/kg of BoNT-A (onaA) into the rat's face markedly reduces the expression of TRPV1 in the trigeminal neurons within two days [17]

BoNT-A (150 kDa) decreases exaggerated and evoked neurotransmitter release from trigeminal ganglion neurons and relieves neuropathic behaviors induced by infraorbital nerve constriction [18]. In infraorbital nerve constriction (IOC) pain model, injection of BoNT-A into the vibrissial pad of the rat reduces face allodynia and dural extravasation following IOC or formalin injection [19]. Others have reported similar pain alleviation with botulinum BoNT-A injection into rats' face—those suffering from facial pain related to IOC [20].

The evidence for a central analgesic effect for BoNT injection in the trigeminal system was provided by Matak et al [21]. These investigators noted that in the formalin-induced facial pain rat model, after facial injection of BoNT-A, the cleaved SNAP-25 (the synaptic protein target of BoNT-A) can be detected in the mesencephalic trigeminal nucleus (trigeminal caudalis nucleus) where it is localized with TRPV1-expressing neurons. BoNT-A injection reduced the c-Fos activation in TNC, as well as locus coeruleus and periaqueductal gray region. Other investigators reported similar findings with BoNT-B [22]. In rats, cultured trigeminal neurons, after exposure to BoNT-A, demonstrate reduction of IL-1β immunoreactivity suggesting an anti-inflammatory effect for this toxin [23]. In mice, after experimental infraorbital nerve damage, unilateral injection of BoNT-A reduces the facial pain behavior bilaterally. Following facial injection of the toxin, investigators observed significant reduction of postprocedure enhanced expression of pro-inflammatory and microglial activation factors [24]. Further support for possible central antinociceptive effect of BoNT-A in trigeminal pain comes from the study of Lyu et al. [25]. They have shown that experimentally induced pain in the tooth pulp of rats increases the expression of nociception-orfanin N/OFQ in rat's trigeminal ganglion. Injection of BoNT-A alleviated facial pain in rats, and it is believed to have worked through changing the expression of nociception-orfanin N/OFQ in the trigeminal ganglia of the studied rats.

In another experiment [26] in rats with trigeminal neuralgia secondary to inferior orbital nerve constriction injury, researchers have shown that facial injection of botulinum toxin type A improved the pain behavior and reduced the expression of transient receptor potential melastatin 3 and transient receptor potential vanilloid type 4, both of which are nociceptive players in the trigeminal subnucleus caudalis.

Human Studies of BoNTs in Trigeminal Neuralgia

Since 2002, several studies have been published on the effect of local botulinum toxin injections in trigeminal neuralgia. The data includes three double-blind, placebo-controlled studies [27–29], one single-blind study [30], and a number of prospective clinical trials and retrospective observations. The four blinded studies [27–30] are discussed next.

Wu et al [27] enrolled 42 patients with trigeminal neuralgia in a 13-weeks, randomized, parallel design, double-blind, placebo-controlled study. Forty patients, 21 in the BoNT and 19 in the saline (placebo) group, completed the study. Botulinum toxinA (Chinese toxin from Lanshou Institute) was diluted in 1cc of normal saline and injected, using a 16 mm long needle, either between the epidermis and dermis or submucosally in the areas affected by pain (Fig. 10.2). Subjects in the BoNT group received 25–75 units and a comparable volume was administered to the subjects in the saline group. Patients remained on the same dose of their medications (carbamazepine, gabapentin, and pregabalin) during the study.

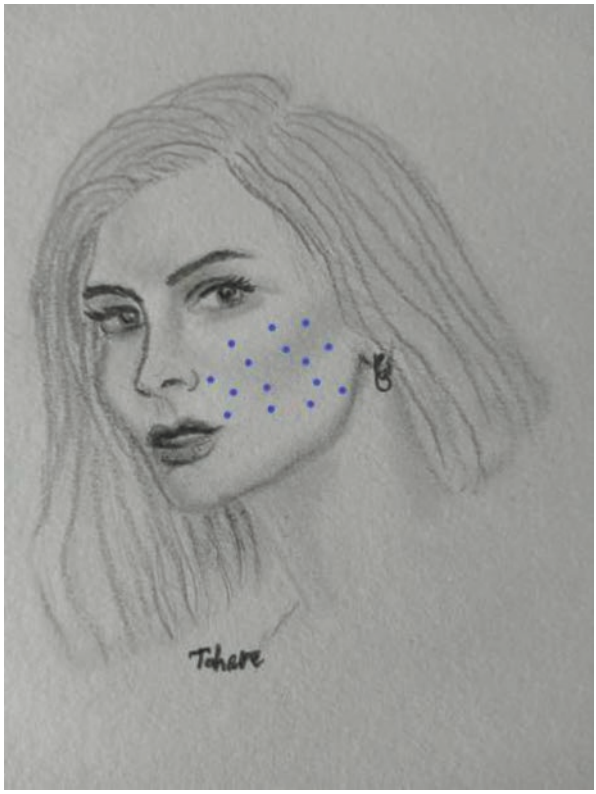

Fig. 10.2 Suggested sites of facial injection in trigeminal neuralgia (15 sites). (Drawn by Tahere Mousavi, MD. From the figure presented in the manuscript published by Wu et al. 2002 [27])

The primary outcome was a significant change in pain frequency and intensity (measured by VAS) compared to placebo. Secondary outcomes were patient global impression of change (PGIC) and proportion of responders defined as those with 50% or more pain reduction compared to baseline. Both primary outcome and all the secondary outcomes improved significantly in the BoNT group compared to the placebo ($P < 0.001$). Side effects were noted in the subjects who received BoNT; seven developed mild facial asymmetry which disappeared after seven weeks and three developed local facial swelling which subsided in a week.

In another double-blind, placebo-controlled study, Zhang et al [28] investigated and compared the efficacy of two doses of botulinum toxinA (Chinese toxin)—25 and 75 units—in 80 patients with trigeminal neuralgia. The study had also a third arm (placebo arm) that included 28 patients. The technique of injection was identical to the first blinded study described above [27]. They included in the study, patients with mean VAS score of 6 and mean number of pain attacks/day of 4 or more. In all patients, the duration of TN exceeded four months.

Primary outcomes were assessed over eight weeks without altering the patients' existing medications (carbamazepine, gabapentin, and opioids):

1. Assessment of pain severity by VAS and pain attack frequency from baseline to endpoint.
2. Patient perception of improvement assessed by Patient Global Impression of Change (PGIC) scale (1–7 scale)
3. Determination of proportion of responders, defined as those with ≥ 50% reduction in mean pain score from baseline to endpoint

As to the VAS assessment, both 25 unit and 75 unit groups significantly improved the pain scores from week 1 to week 8 post injection compared to the placebo group ($P < 0.01$) (Fig. 10.3); there was no significant efficacy difference between the two groups ($P < 0.05$). Regarding the proportion of responders at week 8 post injection, the figures were 70.4% for the 25U group and 86.2% for the 75U group—both were significantly higher than the placebo group (32.1%) ($P < 0.017$). There was no significant difference between the 25U and 75U groups ($P > 0.05$). PGIC score was improved or significantly improved—66.7% in toxin and 23.1% in the placebo group ($P < 0.01$), but again, there was no significant difference between the two groups with different toxin doses. Two patients in the 25 unit-toxin group developed transient edema at the side of injection that resolved within five days.

In the third double-blind, placebo-controlled study, Zuniga et al [29] tested the effect of onabotulinumtoxinA in 36 patients with trigeminal neuralgia unresponsive to conventional therapy for TN.

Patients presented with pain in V2 and V3 distributions. In the toxin group (20 patients), those who had pain in V2 distribution received a total of 50 units injected subcutaneously and distributed over 16–18 sites, 1 cm apart. Those patients with additional V3 distribution received another 10 units into the ipsilateral masseter muscle. Patients in the saline group received the same volume of normal saline (1cc). At two months after toxin injection, the VAS score showed a trend toward significance in the OnaA group ($P = 0.07$), but at three months, the VAS score was

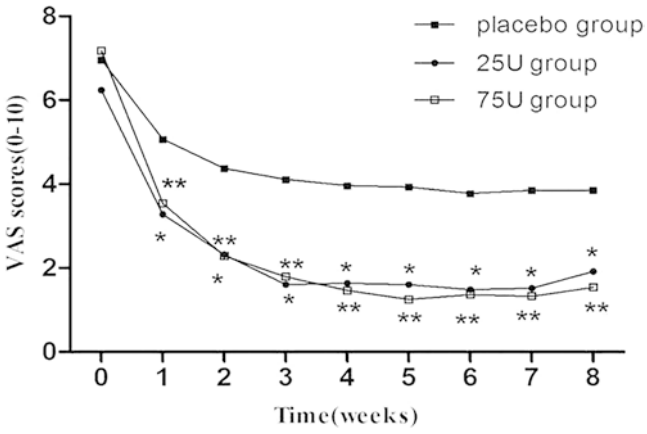

Fig. 10.3 The VAS response curves of patients with TN to BoNT-A injection over 8 weeks comparing the effects of two doses of the BoNT-A with each other and placebo over 8 weeks. (From Zhang et al. 2014, J Headache and Pain. Reproduced by permission from PMC under creative commons attribution license)

significantly lower in the onaA group compared to placebo (P = 0.01). Regarding pain paroxysms, both at two months and three months after toxin injection, the reduction in number of pain attacks was significantly more in the toxin group (P = 0.02 and P = 0.01).

In the single-blind study of Shehata et al [30], 20 subjects with TN were randomized into BoNT-A and placebo groups. In the BoNT-A group subjects received subcutaneous injections of 40–60 units of onabotulinumtoxinA into 8 to 12 points (5 units per point) in the face. Primary outcome was a decrease in pain intensity at 12 weeks measured by VAS compared to the placebo. At 12 weeks, the onaA group demonstrated a reduction of 6.5 points in VAS compared to 3 points in the placebo group (P = 0.0001). As a secondary outcome, quality of life also improved significantly among patients in the BoNT-A group; more patients in the BoNT-A group were able to reduce the number of their pain medications.

In agreement with abovementioned blinded studies, several non-blinded, prospective, and retrospective studies have suggested that subcutaneous or intradermal injections of BoNTs reduces intensity of pain in trigeminal neuralgia, as well as reducing the frequency of pain attacks [31–44]. Among patients with trigeminal neuralgia, individuals older than 70 or 80 years respond to toxin therapy similar to individuals who are younger than 60 years of age; BoNT injections may be a more reasonable approach in elderly who are sensitive to high doses of drugs such as carbamazepine, oxcarbazepine, baclofen, and gabapentin [43, 44] often used in TN.

Long-term studies of BoNT therapy in TN are scarcely available. In a study of 88 patients, Li et al [40] assessed the efficacy and duration of the efficacy of treatment over 14 months. One month after the first treatment, close to 90% of the patients demonstrated reduction of both facial pain and frequency of pain attacks. The treatment remained effective after each injection (every three months); at the end of the study, 25% of patients were free from facial pain.

Over the past few years, alternative injection techniques have been proposed for BoNT treatment of trigeminal neuralgia. One such technique is injecting the toxin into the sphenopalatine ganglion (SPG) [45–46]. In one study of 10 patients [45], Yoshida injected 50 units of botulinum toxinA into the SPG using a special CAD-CAM guide used in dentistry. He found that both mean VAS representing pain intensity and mean pain frequency of the studied group improved significantly after the toxin injection ($P < 0.01$) (6.1 and 19.4 pre-injection values changed to 1.9 and 5.4 post injection, respectively). The procedure was considered safe by the investigator. In another study of nine patients with TN [46], injection of 25 units of onabotulinumtoxinA into SPG reduced the pain intensity by 50% in four of nine patients and, in two additional patients, led to complete pain remission. However, pain frequency did not change significantly in the majority of patients.

The literature in secondary trigeminal neuralgia is limited to anecdotal case reports. There are reports of patients with TN secondary to multiple sclerosis or caused by facial trauma in whom local injection of BoNT into the facial pain region alleviated patient's discomfort [47, 48]. The following case is from the author's experience with BoNT therapy in a recalcitrant post-traumatic case of trigeminal neuralgia.

Case Report

A 41-year-old woman was referred to the Yale Botulinum Neurotoxin Treatment Clinic for consideration of BoNT therapy for a disabling trigeminal neuralgia. She developed severe left-sided facial pain and headaches following a car accident 20 years earlier. The pain was dull and deep at first but gradually transformed into bouts of sharp and jabbing pain lasting 15–20 seconds. Many factors provoked pain, especially exposure to cold environment. She reported several trigger points close to the nose and corner of the mouth, making application of make-up difficult. In "bad days," pain affected the region around the left eye and made it "twitch."

Patient had tried multiple medications for the pain including beta blockers, antiepileptic drugs, calcium channel blockers, nonsteroidal anti-inflammatory drugs, oxycodone, and acupuncture. She had had three surgical procedures in the past including decompression surgery via retro-mastoid craniotomy for relieving pressure upon the trigeminal nerve, exploration for possible CP angle pathology (second surgery), and cortical stimulation for pain relief. None of the three procedures relieved her pain. Patient described constant daily facial pain with superimposed bouts of sharp pain. Past medical, family, and social history disclosed no issues of concern.

On examination, several trigger points were identified on the left side of the face close to the nose and left corner of the mouth. A total of 30 units of onaA were injected subcutaneously in 20 sites (1.5 units per site) into the V2 distribution. In addition, another 10 units (4 points) were injected into the left frontalis (2.5 units, 4 sites) and five units into anterior temporal region (2.5 units at two points) (Fig. 10.4).

After two weeks, patient reported marked reduction in severity of pain (from level 9 in VAS to level 2) and 90% reduction in the frequency of sharp pains. This response lasted for five months at which time the severity of pain returned and required another injection that produced a similar effect. No side effects were reported. Patient described her experience as very satisfactory in the Patient Global Impression of Change (PGIC) scale 1–7 (7 being very satisfactory).

Comment

Using the criteria of the Assessment Subcommittee of the American Academy of Neurology [49, 50], BoNT-A is efficacious (level A efficacy) for treatment of primary (classic) trigeminal neuralgia; based on two class I studies [27, 28]. As to the number of injections and effective dose, 15–20 subcutaneous facial injections with 1.5–2 units injected per each site seems a reasonable and effective approach [27, 28]. The treatment seems safe and is well tolerated. Minor facial asymmetry, a common side effect of the procedure, is accepted by the patients who are suffering from disabling bouts of pain; it is transient and resolves within weeks. In the the authors' experience, out of the eight patients with recalcitrant trigeminal neuralgia, six

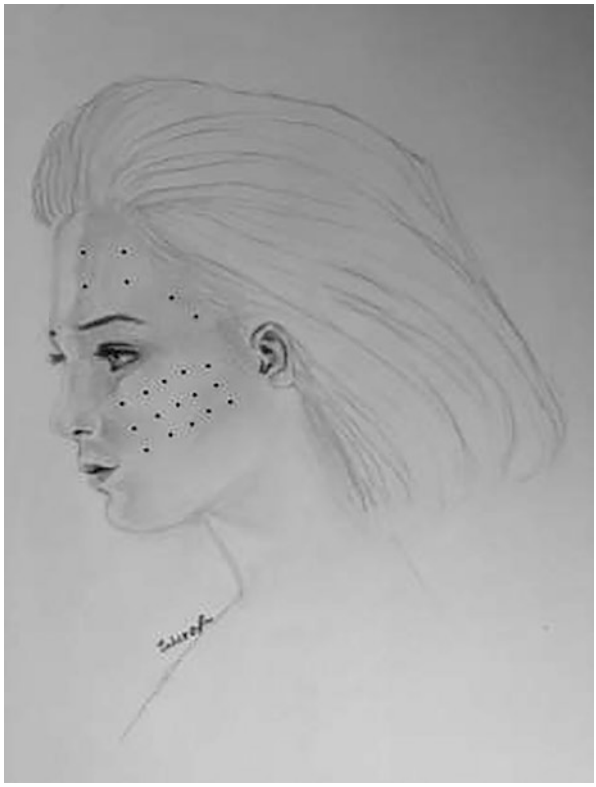

Fig. 10.4 Sites of onabotulinumtoxinA injections in case report with recalcitrant trigeminal neuralgia

patients had either satisfactory or very satisfactory response and the other two failed to respond.

Blinded studies are needed in the area of secondary trigeminal neuralgia (e.g., in multiple sclerosis) where case reports suggest good response after BoNT therapy (see above). Admittedly, blinded studies in this area would be hard to do due to the small number of available patients.

Recently, there are reports from open label studies in small groups of patients claiming significant improvement of trigeminal neuralgia after BoNT-A injection into sphenopalatine ganglion [45, 46]. Although this technique is more cumbersome than subcutaneous facial injections of BoNT, blinded studies with sham injections into SPG are needed to confirm the efficacy of this mode of treatment in trigeminal neuralgia.

Temporomandibular Disorder (TMD)

Temporomandibular joint disorders are a group of conditions related to pathological processes which affect the jaw and muscles of mastication [51]. Temporomandibular disorders may be myogenic or arthrogenic depending on the source of pathology.

The former arises from myofascial involvement of masseter, lateral pterygoid, and temporal muscles, while the latter originates from pathology of temporomandibular joint. TMD is a common ailment, affecting 5–12% of the population [52]. Manfredini et al [53] reported the prevalence of TMD based on TMD's underlying pathology: Disc disease 25%, myofascial masseter pain 12.9%, and inflammatory pain of temporomandibular joint 8.9%. In a majority of patients, however, the underlying pathology is difficult to discern with certainty.

Pain is a major symptom of TMD. It can be localized to the temporomandibular joint with local tenderness on palpation, or it may be felt over the masseters as a myofascial pain syndrome. Some patients present with limitation of jaw opening often associated with disturbing jaw pain. In the case of a dislocated joint, the patient often experiences a clicking sound at the region of the joint upon jaw movements. Associated headache is not uncommon and could take the form of tension or migraine headaches. Schiffman et al [54] indicated a sensitivity of 89% with specificity of 87% ($P < 0.001$) for the following two criteria in TMD headache: (1) temple area headache that changes with jaw movement and (2) provocation of headache by temporalis muscle palpation or jaw movement. Limitation of jaw opening can be confused with dystonia of jaw opening—a form of focal dystonia which also may cause pain. Additional forms of facial pain in TMDs also occur that at times take the form of sharp, fleeting pains, and can be confused with trigeminal neuralgia. The differential diagnosis includes other common conditions such as pain of sinusitis or root and muscle pain related to cervical osteoarthritis. The condition is often difficult to diagnose due to the overlap of symptomatology with aforementioned facial and neck pain disorders. Graff-Radford and Bassiur [55] suggest that clinicians should strongly consider the diagnosis of TMD if at least three of the following four features exist: (1) pain in the pre-auricular and temporal region brought on by functions such as chewing; (2) pain on palpation over the TMJ; (3) joint noise such as clicking, popping, or crepitus; and (4) limited range of motion of the TMJ.

Treatment

The first line of treatment for TMD includes noninvasive measures such as massage, warm compresses, and physical therapy. Physical therapy encompasses posture training exercises, joint mobilization, orthotic devices, and splint therapy. Other modes of treatment, such as electrotherapy, ultrasound, laser therapy, and acupuncture, have also been employed, but their efficacy is in question [54]. Pharmacological agents such as nonsteroidal, anti-inflammatory drugs, muscle relaxants, tricyclic antidepressants, and antiepileptic analgesics (gabapentin, pregabalin) may provide partial relief. Opioid analgesics are used for recalcitrant pain but significant relief occurs only in half of the patients with noncancer-related pain [56]. Acute pain related to TMD may require intra-articular injection of lidocaine, hyaluronic acid, or corticosteroids [57]. Surgical intervention is considered the last resort and, depending on the pathology of TMD, consists of disc repositioning, repair of disc

perforation, disc recontouring, lysis of adhesions, and discectomy [58]. For TM joint arthritis, arthroplasty is sometimes performed [59]. Temporomandibular ankylosis may require resection of the ankylosis block in combination with bilateral coronoidectomy[60].

Botulinum Toxin Treatment of TMD

In 1997, Daelen et al. [61], as well as Moore and Wood [62] independently, reported that botulinum toxin A may prevent TM joint dislocation and relieve TMJ pain in patients with TMD due to masseter and lateral pterygoid spasticity. The former authors described a 56-year-old man with multiple sclerosis and frequent dislocation of TM joint due to spasticity in whom administration of onaA into the masseter and lateral pterygoid muscles resulted in correction of dislocation and pain relief. The positive results lasted for four months and were reproducible with repeat injections. The patient reported by Moore and Wood [62] received 75 units of onaA into each lateral pterygoid muscle and had similar results lasting for 10 months.

Over the past 20 years, several open label retrospective studies have reported positive results of BoNT therapy in TMD supporting the results of earlier observations [63, 64, 65, 66, 67, 68, 69, 70, 71, 72]. Among the open label studies, the strongest support for the use of BoNTs in TMD comes from the observations of Song, Freund, and Blitzer in 200 patients treated in hospitals affiliated with Columbia University in New York City and Harvard Medical School in Boston [73]. In this population, they reported a success rate of 60% with onabotulinumtoxinA injection in temporomandibular disorder [73]. Their protocol required injection of both masseter and temporalis muscles. Each masseter was injected with a total of 50 units at 5 points, whereas each temporalis muscle was injected in four points [Fig. 10.5].

Lateral pterygoid muscles [LP] are another target for treatment of temporomandibular joint disorders. Lateral pterygoid muscle helps in protrusion of the jaw and is often involved in producing symptoms of TMD. Blitzer prefers intra-oral injection of LP guided by electromyography. The advocated dose of onabotulinumtoxinA for intra-oral injection of lateral pterygoid in TMD is 7.5–10 units for each side [74]. MRI-guided LT injections may provide better precision [75].

Three published blinded studies have provided data on the efficacy of BoNT injections in TMD. In one study [76], 24 patients with TMD with symptoms referable to the masseters and temporalis muscles were randomized to BoNT-A and saline groups. The investigators injected onabotulinumtoxinA (Botox) under electromyographic guidance into the masseter (3 sites, 10 units per site) and temporalis (two sites, 10 units per site) muscles. Patients were evaluated with a biobehavioral questionnaire that included assessment of pain (questions 5–7), disability (questions 11–13) and psychosocial status (questions 20) at baseline, 14 and 28 days after injection. Compared with baseline, only question 20 (at 28 days after injection) noted a trend for psychological improvement in the toxin group ($P = 0.06$). The

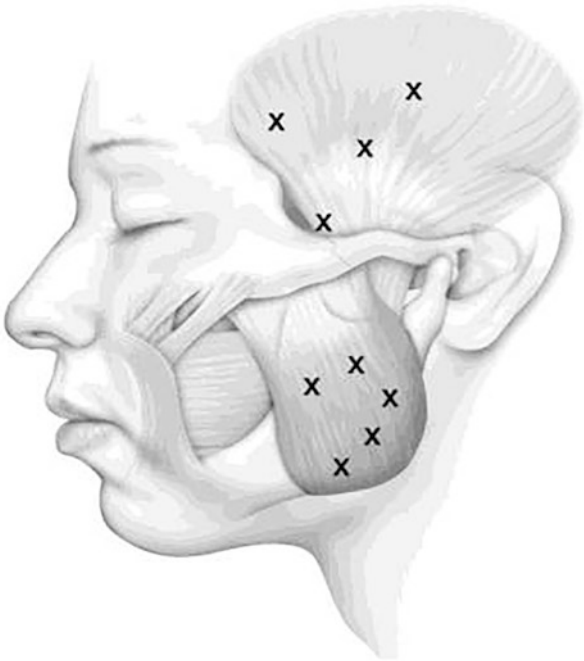

Fig. 10.5 Sites of temporal and masseter injections advocated by Dr. Blitzer et al. and his colleagues for treatment of TMD. (Published by Mor et al. in Toxins 2015. Reproduced for publication under creative commons attribution license)

placebo group showed several trends toward significance; the placebo results showed significance (P = 0.027) for improvement of disability at day 14 post injection.

Ernberg et al. [77] conducted a double-blind, crossover multicenter study on 21 patients with TMD who met the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) [78]. The group was heterogeneous, but most patients had myofascial pain in the masseter region. A total of 50 units of BoNT-A (onaA) were injected into the masseter muscles. Subjects were tested with a variety of scales for pain, quality of life, and psychosocial effects. Regarding pain, a 30% decrease in VAS was considered significant since this degree of pain reduction has been shown to correspond to a "much improved" state reported by patients in the patient global impression of change (PGIC); 50% reduction would correspond to "very much improved" [79]. Weekly change in VAS (30% or more) was considered as the primary outcome of the study. Both onaA and placebo improved pain by 30% or more, but the difference between the two groups was not statistically significant. Authors mentioned several shortcomings of the study which included the small number of patients and injections limited to the masseter muscles.

Patel et al [80] conducted a double-blind, placebo-controlled study with incobotulinumtoxinA (incoA) injections in 20 patients with TMD. The design of the study was crossover. The authors hypothesized that TMD of their patients was due to hyperfunction or spasms of masseter, temporalis, and lateral pterygoid muscles. IncoA was injected bilaterally into masseter (50 units/side), temporalis (25 units/

side), and lateral pterygoid (10 units/side) muscles. The total dose per patient was 170 units. The primary outcome of the study was a significant decrease in pain scale (VAS, 1–10) in the toxin group compared to placebo. Pain measured by VAS and pressure-induced tenderness of the temporalis muscle were assessed at baseline and then every four weeks up to week 16 post injection. Four weeks after injection, the difference in reduction of pain score between incoA and placebo group was statistically significant. The mean VAS reduction (scale of 1–10) was 4.5 for incoA and 1.7 for the placebo group ($P = 0.009$). The average pain score for weeks 2, 3, and 4 post injection remained also significantly lower for toxin group when compared to baseline. For composite masticatory muscle pain to palpation score, at one month post injection, the muscle pain on palpation was significantly reduced in the onaA group compared to the saline group ($P = 0.003$).

Several communications have indicated the usefulness of BoNT injections in TMD in conjunction with surgical procedures and surgical intervention. In a study of 20 patients with TM pain and TM joint ankylosis, injection of BoNT-A into masticator muscles led to reduction of pain during post-surgical physiotherapy [81]. Altaweel et al [82] have found intra-oral injection of lateral pterygoid muscle helpful in reducing pain and discomfort associated with TM joint disc displacement requiring reduction surgery [82]. Yoshida [83], in a study of 32 patients with recurrent TM joint dislocation, also found injection of BoNT-A into lateral pterygoid muscle effective and safe specifically in the group with habitual dislocation (versus neurogenic dislocation). In another study [84] of 52 patients, injection of the masseter and temporalis muscles with BoNT-A led to significant reduction of pain associated with arthroplasty compared to the control group ($P = 0.04$). Other investigators have found that injection of botulinumtoxin-A into the masseter and temporalis muscles improves pain scores (measured by VAS) and maximum interincisal opening (MIO) when used as an adjunct to arthrocentesis in patients with TMD [85].

In a retrospective review of 25 patients who received BoNT injections for treatment of TMD, the authors found that those with localized pain were better responders than those with referred pain (69% vs. 16.7% $P = 0.017$) [86]. No serious side effects were mentioned in the above-discussed studies of BoNT injections in TMD [60–86]. Most authors commented specifically on the safety of this mode of therapy.

Recently, few studies have reported on mandibular bone loss after injection of BoNTs into the massater muscles for TMD [87–89]. Raphael et al [87] were the first group to report this issue. They compared the bone density of jaw tubercle in seven patients who had two or more injections of BoNT into masseter muscles for TMD with nine patients who did not have BoNT injections. All seven patients in the BoNT injected group demonstrated reduced bone density, whereas none in the control group had any such reduction. Balant-Melo et al [88] studied the bone density of condylar bone in mice after injection of BoNT into the masseter muscle. Two weeks after injection, the authors noted significant bone loss in the mandibular condyle ipsilateral to the masseter injection, whereas the massater injection with saline on the contralateral side caused no bone loss. These authors, in a later communication [89], reviewed the literature on the issue of mandibular bone loss after BoNT injection into the masseter muscle and discussed in detail the involved metabolic

mechanisms. They suggested that, based on the animal data from the literature, the potential for mandibular bone loss needs to be mentioned to the patients before contemplating botulinum toxin injections into the masseter muscle for TMD treatment.

Comment

The data from open label studies [61–75] strongly suggest that BoNT injections into masseter, temporalis, and lateral pterygoid muscles alleviate spontaneous and pressure-induced jaw pain and function in patients with TMD; furthermore, in the applied doses, these injections are devoid of serious side effects. Some studies have even found improvement of quality of life in patients with TMD after BoNT injections into masseter and temporalis muscles [90]. Surprisingly, the number of blinded and placebo-controlled studies in this common and disabling pain disorder is very limited (only 3) [76, 77, 80]. The results of these studies indicate modest improvement of pain and function after BoNT injections. There are, however, issues with these studies that interfere with proper interpretation of the data. Two studies [76, 77] have shown a strong placebo effect, a factor that clouds conclusions about the toxin effect assessment. In one study [77], injections were limited to the masseter muscle only. All three studies have been conducted in a small number of patients. In the study of Patel et al [80], the toxin group (incoA) demonstrated significant pain reduction at four weeks post injection compared to placebo, while at weeks 8,12, and 16, both toxin and placebo significantly reduced pain (albeit the response was stronger in the toxin group); the difference between the two groups after week 4 was not statistically significant. If the study group were larger, the response beyond four weeks might have reached significance in the toxin group.

Our experience at Yale over 12 years with a sizeable number of patients (approximately 100) agrees with the experience of Blitzer group (200 patients) from Columbia University [73] in which 50–60% of patients with recalcitrant oromandibular disorder experience satisfactory pain relief and improvement of jaw function after botulinum toxin injections [Patient 10-2]. The injections need to include both masseter and temporalis muscles. Additional injection of lateral pterygoid is also desirable. The dose in the case of onabotulinumtoxinA for each masseter muscle is 40–50 units, and 25–30 units for each temporalis muscle. In the case of pterygoid muscle, 7.5–10 units per side are advocated for intra-oral injection [73]. In most of our patients, we injected the lateral pterygoid extraorally, identifying the muscle by palpation (upon jaw opening) or EMG slightly anterior to the temporomandibular joint and below the posterior rim of the zygomatic arch. For extraoral injection, we have used 20 units per pterygoid muscle. In our experience, also noted by others, the injections caused no serious side effects in TMD and were tolerated well by the patients.

There is clearly a need for multicenter, randomized, double-blind, placebo-controlled studies in order to establish the efficacy of BoNT injections in TMD. Such

studies, when conducted in large cohorts can look specifically into BoNT action in subgroups of TMD such as those with strictly myofascial pain, those with surgical indications (subluxation, arthrosis, ankylosis), and so forth. Such large, multicenter studies should employ the technique and doses which have already been reported to be effective in sizeable, carefully designed open label observations [73]. The issue of mandibular bone loss after masseter injection [87, 88, 89] also deserves attention and further exploration.

In recent years, several review articles, some of which included or attempted data meta-analysis, have been published on the subjects of BoNT therapy in TMD [90–95]. A majority of these reviews acknowledge the encouraging data from the current literature regarding treatment of TMD symptoms with BoNTs, but also emphasize the need for multicenter, blinded, placebo-controlled studies in this area.

Other important causes of pain in trigeminal distribution such as bruxism and dental pain are discussed in Chap. 17 (Botulinum Toxin Treatment in Dentistry) of this book.

Case Report (10-2)

A 29-year-old female visited the Yale Botulinum Toxin Treatment Clinic for evaluation of jaw stiffness, tenderness over right masseter, temporomandibular joint, and right-sided headaches. She noted the onset of her symptoms about 8 years ago. The symptoms gradually increased in severity. The headaches, in particular, became disabling occurring almost daily with marked exacerbations several times per week. During swallowing and chewing, she often heard a clicking sound bilaterally. Treatment with a variety of analgesic medications including tricyclic antidepressants, nonsteroidal anti-inflammatory agents, and anti-epileptic drugs failed to relieve the pain. She did not smoke or drink alcohol and did not use illicit drugs.

The general medical examination was normal. Opening and closing of the jaw caused discomfort. The regions of right masseter and temporalis muscles were tender to touch. Neurological examination including assessment of cognition, cranial nerves, motor and sensory systems, cerebellar testing, speech, gait, stance, and reflexes was normal. A detailed ear-nose and throat evaluation showed no abnormality. Imaging studies of the brain and TM joints were normal. OnaA was injected bilaterally into the masseter and temporalis muscles (Fig. 10.6). The dose per masseter muscle was 40 units (divided into two 20-unit injections at two sites), while the dose per temporalis muscle was 20 units per side (two injections, each 10 units). A week after the injection, the patient reported marked reduction of jaw stiffness, masseter pain, and headaches denoting 90% improvement of her symptoms. In global impression of change (1–7 scale), her impression was 7 (very much improved). The improvement lasted for three months. Repeat injections over a year of follow-up (every 4 months) had the same effect.

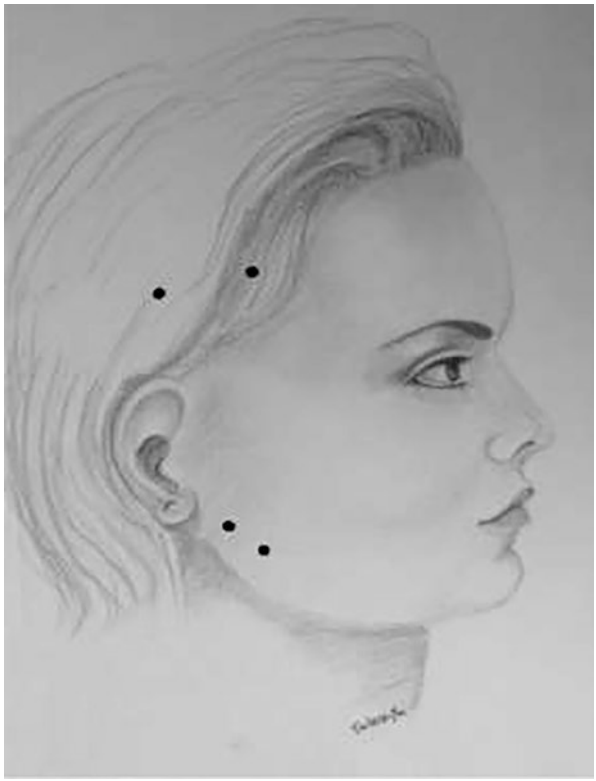

Fig. 10.6 Site of BoNT-A injections for relieving pain in temporomandibular disorder. (patient 10-2). (Drawing courtesy of Tahere Mousavi, M.D)

References

1. 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.
2. Cruccu G, Finnerup NB, Jensen TS, Scholz J, Sindou M, Svensson P, Treede RD, Zakrzewska JM, Nurmikko T. Trigeminal neuralgia: new classification and diagnostic grading for practice and research. Neurology. 2016; 87(2):220–8. https://doi.org/10.1212/WNL.0000000000002840. Epub 2016 Jun 15. PMID: 27306631; PMCID: PMC4940067
3. Manzoni GC, Torelli P. Epidemiology of typical and atypical craniofacial neuralgias. Neurol Sci. 2005;26(Suppl 2):s65–7.
4. Bangash TH. Trigeminal neuralgia: frequency of occurrence in different nerve branches. Anesth Pain Med. 2011;1(2):70–2.
5. Headache Classification Subcommittee of the international headache Society. The international classification of headache disorders, vol. 38. 3rd ed. Cephalalgia; 2018. p. 1–2121.
6. Obermann M. Treatment options in trigeminal neuralgia. Ther Adv Neurol Disord. 2010;3(2):107–15.
7. Fromm GH, Terrence CF, Chattha AS. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. Ann Neurol. 1984;15:240–4.
8. Veerapaneni KD, Kapoor N, Veerapaneni P, Nalleballe K. Trigeminal neuropathy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jul 26. 2021 Jan. PMID: 32310586.

9. Zhao C, Shrestha N, Liu H, Shen Y, Meng L, Fan B, Luo F. The PATCH trial: efficacy and safety of 5% lidocaine-medicated plaster for the treatment of patients with trigeminal neuralgia: a study protocol for a multicentric, double-blind, enriched enrolment randomised withdrawal, vehicle-controlled study. BMJ Open 2021; 11(8):e045493. https://doi.org/10.1136/bmjopen-2020-045493. PMID: 34341037; PMCID: PMC8330571.
10. Zakrzewska JM, McMillan R. Trigeminal neuralgia: the diagnosis and management of this excruciating and poorly understood facial pain. Postgrad Med J 2011; 87(1028):410–6. https://doi.org/10.1136/pgmj.2009.080473. Epub 2011 Apr 14. PMID: 21493636.
11. Shankar Kikkeri N, Nagalli S. Trigeminal neuralgia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. 2021 Jan. PMID: 32119373.
12. Lambru G, Zakrzewska J, Matharu M. Trigeminal neuralgia: a practical guide. Pract Neurol. 2021 Jun 9: practneurol-2020-002782. https://doi.org/10.1136/practneurol-2020-002782. Epub ahead of print. PMID: 34108244.
13. Araya EI, Claudino RF, Piovesan EJ, Chichorro JG. Trigeminal neuralgia: basic and clinical aspects. Curr Neuropharmacol. 2020;18(2):109–19. https://doi.org/10.2174/1570159X17666191010094350. PMID: 31608834; PMCID: PMC7324879
14. Borges A, Casselman J. Imaging the trigeminal nerve. Eur J Radiol 2010 74(2):323–40. https://doi.org/10.1016/j.ejrad.2010.02.006. Epub 2010 Mar 12. PMID: 20227216.
15. Durham PL, Cady R, Cady R. Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache. 2004;44:35–42.
16. Meng J, Ovsepian SV, Wang J, Pickering M, Sasse A, Aoki KR, Lawrence GW, Dolly JO. Activation of TRPV1 mediates calcitonin gene-related peptide release, which excites trigeminal sensory neurons and is attenuated by a retargeted botulinum toxin with anti-nociceptive potential. J Neurosci 2009; 29(15):4981–92. https://doi.org/10.1523/JNEUROSCI.5490-08.2009. PMID: 19369567; PMCID: PMC6665337.
17. Shimizu T, Shibata M, Toriumi H, Iwashita T, Funakubo M, Sato H, Kuroi T, Ebine T, Koizumi K, Suzuki N. Reduction of TRPV1 expression in the trigeminal system by botulinum neurotoxin type-A. Neurobiol Dis 2012; 48(3):367–78. https://doi.org/10.1016/j.nbd.2012.07.010. Epub 2012 Jul 20. PMID: 22820141.
18. Kitamura Y, Matsuka Y, Spigelman I, Ishihara Y, Yamamoto Y, Sonoyama W, Kamioka H, Yamashiro T, Kuboki T, Oguma K. Botulinum toxin type a (150 kDa) decreases exaggerated neurotransmitter release from trigeminal ganglion neurons and relieves neuropathy behaviors induced by infraorbital nerve constriction. Neuroscience. 2009; 159(4):1422–9. https://doi.org/10.1016/j.neuroscience.2009.01.066. Epub 2009 Feb 3. Erratum in: Neuroscience. 2009 Jul 7; 161(3):950. Kamioka, H [added]; Yamashiro, T [added]. PMID: 19409226.
19. Filipović B, Matak I, Bach-Rojecky L, Lacković Z. Central action of peripherally applied botulinum toxin type A on pain and dural protein extravasation in rat model of trigeminal neuropathy. PLoS One. 2012;7(1):e29803. https://doi.org/10.1371/journal.pone.0029803. Epub 2012 Jan 4. PMID: 22238656; PMCID: PMC3251614
20. Matsuka Y, Yokoyama T, Yamamoto Y, Suzuki T, Dwi Fatmawati NN, Nishikawa A, Ohyama T, Watanabe T, Kuboki T, Nagai A, Oguma K. Application of purified botulinum type a neurotoxin to treat experimental trigeminal neuropathy in rats and patients with urinary incontinence and prostatic hyperplasia. J Toxicol. 2012;2012:648384. https://doi.org/10.1155/2012/648384. Epub 2012 Jun 14. PMID: 22745637; PMCID: PMC3382382
21. Matak I, Rossetto O, Lacković Z. Botulinum toxin type A selectivity for certain types of pain is associated with capsaicin-sensitive neurons. Pain 2014; 5(8):1516–1526. https://doi.org/10.1016/j.pain.2014.04.027. Epub 2014 May 2. PMID: 24793910.
22. Ramachandran R, Lam C, Yaksh TL. Botulinum toxin in migraine: role of transport in trigemino-somatic and trigemino-vascular afferents. Neurobiol Dis. 2015; 79:111–22. https://doi.org/10.1016/j.nbd.2015.04.011. Epub 2015 May 6. PMID: 25958249; PMCID: PMC4458441.

23. Edvinsson J, Warfvinge K, Edvinsson L. Modulation of inflammatory mediators in the trigeminal ganglion by botulinum neurotoxin type A: an organ culture study. J Headache Pain. 2015; 16:555. https://doi.org/10.1186/s10194-015-0555-z. Epub 2015 Aug 6. PMID: 26245187; PMCID: PMC4526514.
24. Chen WJ, Niu JQ, Chen YT, Deng WJ, Xu YY, Liu J, Luo WF, Liu T. Unilateral facial injection of Botulinum neurotoxin A attenuates bilateral trigeminal neuropathic pain and anxiety-like behaviors through inhibition of TLR2-mediated neuroinflammation in mice. J Headache Pain 2021; 22(1):38. https://doi.org/10.1186/s10194-021-01254-2. PMID: 34000998; PMCID: PMC8130347.
25. Lyu J, Wen J, Guo R, Zhu Y, Liang H, Gao M, Wang H, Lai W, Long H. Botulinum toxin A alleviates orofacial nociception induced by orthodontic tooth movement through nociceptin/orphanin-FQ pathway in rats. Arch Oral Biol 2020; 117:104817. https://doi.org/10.1016/j.archoralbio.2020.104817. Epub 2020 Jun 12. PMID: 32603879.
26. Zhang Y, Su Q, Lian Y, Chen Y. Botulinum toxin type A reduces the expression of transient receptor potential melastatin 3 and transient receptor potential vanilloid type 4 in the trigeminal subnucleus caudalis of a rat model of trigeminal neuralgia. Neuroreport 2019 30(10):735–740. https://doi.org/10.1097/WNR.0000000000001268. PMID: 31116130.
27. Wu CJ, Lian YJ, Zheng YK, Zhang HF, Chen Y, Xie NC, Wang LJ. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia 2002; 32:443–450.
28. Zhang H, Lian Y, Ma Y, Chen Y, He C, Xie N, Wu C. 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. https://doi.org/10.1186/1129-2377-15-65. PMID: 25263254; PMCID: PMC4194456.
29. Zúñiga C, Piedimonte F, Díaz S, Micheli F. Acute treatment of trigeminal neuralgia with onabotulinum toxin A. Clin Neuropharmacol 2013; 36(5):146–150. https://doi.org/10.1097/WNF.0b013e31829cb60e. PMID: 24045604.
30. Shehata HS, El-Tamawy MS, Shalaby NM, Ramzy G. Botulinum toxin-type A: could it be an effective treatment option in intractable trigeminal neuralgia? J Headache Pain 2013; 14:92.
31. Turk U, Ilhan S, Alp R, Sur H. Botulinum toxin and intractable trigeminal neuralgia. Clin Neuropharmacol 2005; 28:161-162
32. Piovesan EJ, Teive HG, Kowacs PA, Della Coletta MV, Werneck LC, Silberstein SD. An open study of botulinum-A toxin treatment of trigeminal neuralgia. Neurology 2005; 65:1306–1308.
33. Zuniga C, Diaz S, Piedimonte F, Micheli F. Beneficial effects of botulinum toxin type A in trigeminal neuralgia. Arq Neuropsiquiatr 2008; 66:500–503.
34. Bohluli B, Motamedi MH, Bagheri SC, Bayat M, Lassemi E, Navi F, Moharamnejad N. Use of botulinum toxin A for drug-refractory trigeminal neuralgia: preliminary report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011; 11: 47–50
35. Borodic GE, Acquadro MA. The use of botulinum toxin for the treatment of chronic facial pain. J Pain. 2002;3:21–7.
36. Wang SY, Yue J, Xu YX, Xue LF, Xiao WL, Zhang CY. Preliminary report of botulinum toxin type A injection at trigger point for treatment of trigeminal neuralgia: experiences of 16 cases. Shanghai Kou Qiang Yi Xue. 2014;23:117–9.
37. Zhang H, Lian Y, Xie N, Chen C, Zheng Y. Single-dose botulinum toxin type a compared with repeated-dose for treatment of trigeminal neuralgia: a pilot study. J Headache Pain 2017; 18(1):81. https://doi.org/10.1186/s10194-017-0793-3. PMID: 28799056; PMCID: PMC5552618.
38. Xia JH, He CH, Zhang HF, Lian YJ, Chen Y, Wu CJ, Ma YQ. Botulinum toxin A in the treatment of trigeminal neuralgia. Int J Neurosci 2016; 126(4):348-353. https://doi.org/10.3109/00207454.2015.1019624. Epub 2015 Aug 18. PMID: 26000810.
39. Gazerani P, Pedersen NS, Staahl C, Drewes AM, Arendt-Nielsen L. Subcutaneous Botulinum toxin type A reduces capsaicin-induced trigeminal pain and vasomotor reactions in human

skin. Pain 2009; 141(1-2):60–69. https://doi.org/10.1016/j.pain.2008.10.005. Epub 2008 Nov 11. PMID: 19004549.
40. Li S, Lian YJ, Chen Y, Zhang HF, Ma YQ, He CH, Wu CJ, Xie NC, Zheng YK, Zhang Y. Therapeutic effect of Botulinum toxin-A in 88 patients with trigeminal neuralgia with 14-month follow-up. J Headache Pain 2014; 15(1):43. https://doi.org/10.1186/1129-2377-15-43. PMID: 24952600; PMCID: PMC4077143.
41. Türk Börü Ü, Duman A, Bölük C, Coşkun Duman S, Taşdemir M. Botulinum toxin in the treatment of trigeminal neuralgia: 6-Month follow-up. Medicine (Baltimore) 2017; 96(39):e8133. https://doi.org/10.1097/MD.0000000000008133. PMID: 28953646; PMCID: PMC5626289.
42. Caldera MC, Senanayake SJ, Perera SP, Perera NN, Gamage R, Gooneratne IK. Efficacy of botulinum toxin type A in trigeminal neuralgia in a South Asian cohort. J Neurosci Rural Pract. 2018; 9(1):100–105. https://doi.org/10.4103/jnrp.jnrp_346_17. PMID: 29456352; PMCID: PMC5812131.
43. Liu J, Xu YY, Zhang QL, Luo WF. Efficacy and safety of botulinum toxin type A in treating patients of advanced age with idiopathic trigeminal neuralgia. Pain Res Manag 2018; 2018:7365148. https://doi.org/10.1155/2018/7365148. PMID: 29849847; PMCID: PMC5907496.
44. Wu S, Lian Y, Zhang H, Chen Y, Wu C, Li S, Zheng Y, Wang Y, Cheng W, Huang Z. Botulinum toxin type A for refractory trigeminal neuralgia in older patients: a better therapeutic effect. J Pain Res 2019; 12:2177–2186. https://doi.org/10.2147/JPR.S205467. PMID: 31410051; PMCID: PMC6643497.
45. Yoshida K. Sphenopalatine ganglion block with botulinum neurotoxin for treating trigeminal neuralgia using CAD/CAM-derived injection guide. J Oral Facial Pain Headache. 2020 Spring; 34(2):135–140. https://doi.org/10.11607/ofph.2510. Epub 2019 Sep 27. PMID: 31560737.
46. Crespi J, Bratbak D, Dodick DW, Matharu M, Jamtøy KA, Tronvik E. Pilot study of injection of onabotulinumtoxin A toward the sphenopalatine ganglion for the treatment of classical trigeminal neuralgia. Headache. 2019; 59(8):1229–1239. https://doi.org/10.1111/head.13608. Epub 2019 Jul 25. PMID: 31342515; PMCID: PMC6771650.
47. Calejo M, Salgado P, Moreira B, Correia C, Barros J. Botulinum toxin type A injections as an effective treatment of refractory multiple sclerosis-related trigeminal pain – a case report. Headache 2019; 59(8):1379–1381. https://doi.org/10.1111/head.13609. Epub 2019 Aug 19. PMID: 31424566.
48. Yoon SH, Merrill RL, Choi JH, Kim ST. Use of botulinum toxin type A injection for neuropathic pain after trigeminal nerve injury. Pain Med 2010; 11(4):630–632. https://doi.org/10.1111/j.1526-4637.2010.00801.x. Epub 2010 Mar 4. PMID: 20210871.
49. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology 2008; 71(20):1639–1643. https://doi.org/10.1212/01.wnl.0000336535.27773.c0. PMID: 19001255.
50. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology 2008; 71(20):1634–1638. https://doi.org/10.1212/01.wnl.0000336533.19610.1b. PMID: 19001254.
51. Song PC, Schwartz J, Blitzer A. The emerging role of botulinum toxin in the treatment of temporomandibular disorders. Oral Dis. 2007;13:253–60.
52. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF; International RDC/TMD Consortium Network, International association for Dental Research; Orofacial Pain Special Interest Group, International Association for the Study of Pain. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†. J Oral Facial Pain Headache. 2014 Winter; 28(1):6–27. https://doi.org/10.11607/jop.1151. PMID: 24482784; PMCID: PMC4478082.

53. Manfredini D, Guarda-Nardini L, Winocur E, Piccotti F, Ahlberg J, Lobbezoo F. Research diagnostic criteria for temporomandibular disorders: a systematic review of axis I epidemiologic findings. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112:453–62.
54. Schiffman E, Ohrbach R, List T, Anderson G, Jensen R, John MT, Nixdorf D, Goulet JP, Kang W, Truelove E, Clavel A, Fricton J, Look J. Diagnostic criteria for headache attributed to temporomandibular disorders. Cephalalgia 2012; 32(9):683-692. https://doi.org/10.1177/0333102412446312. PMID: 22767961; PMCID: PMC4521766.
55. Graff-Radford SB, Bassiur JP. Temporomandibular disorders and headaches. Neurol Clin. 2014;32:525–37.
56. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage. 1992;7:69–77.
57. Bjornland T, Gjaerum AA, Moystad O. Osteoarthritis of the temporomandibular joint: an evaluation of the effects and complications of corticosteroid injections compared with injection with sodium hyaluronate. J Oral Rehabil. 2007;34:583–9. https://doi.org/10.1111/j.1365-2842.2007.
58. Vallerand WP, Hall MB. Improvement in myofascial pain and headaches following TMJ surgery. J Craniomandib Disord 1991 Summer; 5(3):197–204. PMID: 1812148.
59. Boutault F, Cavallier Z, Lauwers F, Prevost A. Temporomandibular joint arthroplasty for osteoarthrosis: A series of 24 patients that received a uni- or bilateral inter-positional silicone sheet. J Stomatol Oral Maxillofac Surg 2018 Jun; 119(3):199–203. https://doi.org/10.1016/j.jormas.2018.02.004. Epub 2018 Feb 20. PMID: 29471049.
60. Bénateau H, Chatellier A, Caillot A, Diep D, Kün-Darbois JD, Veyssière A. L'ankylose temporo-mandibulaire [Temporo-mandibular ankylosis]. Rev Stomatol Chir Maxillofac Chir Orale. 2016 Sep;117(4):245–255. https://doi.org/10.1016/j.revsto.2016.07.001. French. Epub 2016 Aug 27. PMID: 27481673.
61. Daelen B, Thorwirth V, Koch A. Treatment of recurrent dislocation of the temporomandibular joint with type A botulinum toxin. Int J Oral Maxillofac Surg. 1997;26:458–60.
62. Moore AP, Wood GD. Medical treatment of recurrent temporomandibular joint dislocation using botulinum toxin A. Br Dent J. 1997;183:415–7.
63. Von Lindern JJ. Type A botulinum toxin in the treatment of chronic facial pain associated with temporo-mandibular dysfunction. Acta Neurol Belg. 2001;101:39–41.
64. Freund B, Schwartz M, Symington JM. The use of botulinum toxin for the treatment of temporomandibular disorders: preliminary findings. J Oral Maxillofac Surg 1999 Aug; 57(8):916–920; https://doi.org/10.1016/s0278-2391(99)90007-1. discussion 920-1. PMID: 10437718.
65. Blitzer A, Brin MF, Greene PE, Fahn S. Botulinum toxin injection for the treatment of oromandibular dystonia. Ann Otol Rhinol Laryngol. 1989;98:93–7.
66. Chaurand J, Godínez-Victoria M, Tellez-Girón A, Facio-Umaña JA, Jimenez-Ponce F. Incobotulinum toxin type A for treatment of chronic myofascial pain. J Oral Sci 2020 Dec 23; 63(1):37–40. https://doi.org/10.2334/josnusd.20-0090. Epub 2020 Dec 9. PMID: 33298638.
67. Hosgor H, Altindis S. Efficacy of botulinum toxin in the management of temporomandibular myofascial pain and sleep bruxism. J Korean Assoc Oral Maxillofac Surg 2020 Oct 31 46(5):335–340. https://doi.org/10.5125/jkaoms.2020.46.5.335. PMID: 33122458; PMCID: PMC7609936.
68. Sipahi Calis A, Colakoglu Z, Gunbay S. The use of botulinum toxin-a in the treatment of muscular temporomandibular joint disorders. J Stomatol Oral Maxillofac Surg 2019 Sep; 120(4):322–325. https://doi.org/10.1016/j.jormas.2019.02.015. Epub 2019 Feb 23. PMID: 30807862.
69. Meral SE, Tüz HH, Başlarlı Ö. Evaluation of patient satisfaction after botulinum toxin A injection for the management of masticatory myofascial pain and dysfunction – a pilot study. Cranio. 2021; 39(1):12-16. https://doi.org/10.1080/08869634.2018.1562660. Epub 2019 Jan 2. PMID: 30600786.

70. Ahn J, Horn C, Blitzer A. Botulinum toxin for masseter reduction in Asian patients. Arch Facial Plast Surg. 2004 May–Jun; 6(3):188–191. https://doi.org/10.1001/archfaci.6.3.188. PMID: 15148129.
71. Teemul TA, Patel R, Kanatas A, Carter LM. Management of oromandibular dystonia with botulinum A toxin: a series of cases. Br J Oral Maxillofac Surg 2016 Dec; 54(10):1080–1084. https://doi.org/10.1016/j.bjoms.2016.06.028. Epub 2016 Oct 21. PMID: 27776922.
72. Connelly ST, Myung J, Gupta R, Tartaglia GM, Gizdulich A, Yang J, Silva R. Clinical outcomes of Botox injections for chronic temporomandibular disorders: do we understand how Botox works on muscle, pain, and the brain? Int J Oral Maxillofac Surg 2017 Mar; 46(3):322–327. https://doi.org/10.1016/j.ijom.2016.11.004. Epub 2016 Nov 28. PMID: 27908491.
73. Sinclair CF, Gurey LE, Blitzer A. Oromandibular dystonia: long-term management with botulinum toxin. Laryngoscope 2013 Dec; 123(12):3078–3083. https://doi.org/10.1002/lary.23265. Epub 2013 Oct 5. PMID: 24122897.
74. Blitzer A, Brin MF, Greene PE, Fahn S. Botulinum toxin injection for the treatment of oromandibular dystonia. Ann Otol Rhinol Laryngol 1989; 98:93-97.
75. Pons M, Meyer C, Euvrard E, Weber E, Sigaux N, Louvrier A. MR-guided navigation for botulinum toxin injection in the lateral pterygoid muscle. First results in the treatment of temporomandibular joint disorders. J Stomatol Oral Maxillofac Surg 2019 Jun; 120(3):188–195. https://doi.org/10.1016/j.jormas.2018.11.002. Epub 2018 Nov 16. PMID: 30453102.
76. Kurtoglu C, Gur OH, Kurkcu M, Sertdemir Y, Guler-Uysal F, Uysal H. Effect of botulinum toxin-A in myofascial pain patients with or without functional disc displacement. J Oral Maxillofac Surg. 2008;66:1644–51.
77. Ernberg M, Hedenberg-Magnusson B, List T, Svensson P. Efficacy of botulinum toxin type A for treatment of persistent myofascial TMD pain: a randomized, controlled, double-blind multicenter study. Pain. 2011;152:1988–96.
78. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord. 1992;6:301–55.
79. Farrar JT, Young JP Jr, LaMoreaux WJ, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94:149–58.
80. Patel AA, Lerner MZ, Blitzer A. Incobotulinumtoxin A injection for temporomandibular joint disorder. Ann Otol Rhinol Laryngol. 2017;126(4):328–33. https://doi.org/10.1177/0003489417693013. Epub 2017 Feb 1. PMID: 28290229
81. Shandilya S, Mohanty S, Sharma P, Chaudhary Z, Kohli S, Kumar RD. Effect of preoperative intramuscular injection of botulinum toxin A on pain and mouth opening after surgical intervention in temporomandibular joint ankylosis cases: a controlled clinical trial. J Oral Maxillofac Surg 2020 Jun; 78(6):916–926. https://doi.org/10.1016/j.joms.2020.02.011. Epub 2020 Feb 19. PMID: 32171600.
82. Altaweel AA, Elsayed SA, Baiomy AABA, Abdelsadek SE, Hyder AA. Extraoral versus intraoral botulinum toxin type A injection for management of temporomandibular joint disc displacement with reduction. J Craniofac Surg. 2019;30(7):2149–53. https://doi.org/10.1097/SCS.0000000000005658. PMID: 31232992
83. Yoshida K. Botulinum neurotoxin injection for the treatment of recurrent temporomandibular joint dislocation with and without neurogenic muscular hyperactivity. Toxins (Basel) 2018 Apr 25 10(5):174. https://doi.org/10.3390/toxins10050174. PMID: 29693593; PMCID: PMC5983230.
84. Thomas NJ, Aronovich S. Does adjunctive botulinum toxin A reduce pain scores when combined with temporomandibular joint arthroscopy for the treatment of concomitant temporomandibular joint arthralgia and myofascial pain? J Oral Maxillofac Surg 2017; 75(12):2521–2528. https://doi.org/10.1016/j.joms.2017.04.011. Epub 2017 Apr 19. PMID: 28500876.
85. Ivask O, Leibur E, Akermann S, Tamme T, Voog-Oras Ü. Intramuscular botulinum toxin injection additional to arthrocentesis in the management of temporomandibular joint pain. Oral

Surg Oral Med Oral Pathol Oral Radiol. 2016;122(4):e99–e106. https://doi.org/10.1016/j.oooo.2016.05.008. Epub 2016 May 24. PMID: 27496577

86. Abboud WA, Hassin-Baer S, Joachim M, Givol N, Yahalom R. Localized myofascial pain responds better than referring myofascial pain to botulinum toxin injections. Int J Oral Maxillofac Surg. 2017;46(11):1417–23. https://doi.org/10.1016/j.ijom.2017.04.020. Epub 2017 May 15. PMID: 28521968
87. Raphael KG, Tadinada A, Bradshaw JM, Janal MN, Sirois DA, Chan KC, Lurie AG. Osteopenic consequences of botulinum toxin injections in the masticatory muscles: a pilot study. J Oral Rehabil. 2014;41(8):555–63. https://doi.org/10.1111/joor.12180. Epub 2014 May 17. PMID: 24836732
88. Balanta-Melo J, Torres-Quintana MA, Bemmann M, Vega C, González C, Kupczik K, Toro-Ibacache V, Buvinic S. Masseter muscle atrophy impairs bone quality of the mandibular condyle but not the alveolar process early after induction. J Oral Rehabil 2019 Mar; 46(3):233–241. https://doi.org/10.1111/joor.12747. Epub 2018 Dec 9. PMID: 30468522.
89. Balanta-Melo J, Toro-Ibacache V, Kupczik K, Buvinic S. Mandibular bone loss after masticatory muscles intervention with botulinum toxin: an approach from basic research to clinical findings. Toxins (Basel) 2019 Feb 1; 11(2):84. https://doi.org/10.3390/toxins11020084. PMID: 30717172; PMCID: PMC6409568.
90. Villa S, Raoul G, Machuron F, Ferri J, Nicot R. Improvement in quality of life after botulinum toxin injection for temporomandibular disorder. J Stomatol Oral Maxillofac Surg 2019 Feb; 120(1):2–6. https://doi.org/10.1016/j.jormas.2018.10.007. Epub 2018 Oct 29. PMID: 30385428.
91. Patel J, Cardoso JA, Mehta S. A systematic review of botulinum toxin in the management of patients with temporomandibular disorders and bruxism. Br Dent J 2019 May; 226(9):667–672. https://doi.org/10.1038/s41415-019-0257-z. PMID: 31076698.
92. Ataran R, Bahramian A, Jamali Z, Pishahang V, Sadeghi Barzegani H, Sarbakhsh P, Yazdani J. The role of botulinum toxin A in treatment of temporomandibular joint disorders: a review. J Dent (Shiraz). 2017;18(3):157–64. PMID: 29034269; PMCID: PMC5634354
93. Thambar S, Kulkarni S, Armstrong S, Nikolarakos D. Botulinum toxin in the management of temporomandibular disorders: a systematic review. Br J Oral Maxillofac Surg 2020 Jun; 58(5):508–519. https://doi.org/10.1016/j.bjoms.2020.02.007. Epub 2020 Mar 3. PMID: 32143934.
94. Serrera-Figallo MA, Ruiz-de-León-Hernández G, Torres-Lagares D, Castro-Araya A, Torres-Ferrerosa O, Hernández-Pacheco E, Gutierrez-Perez JL. Use of botulinum toxin in orofacial clinical practice. Toxins (Basel) 2020 Feb 11; 12(2):112. https://doi.org/10.3390/toxins12020112. PMID: 32053883; PMCID: PMC7076767.
95. Machado D, Martimbianco ALC, Bussadori SK, Pacheco RL, Riera R, Santos EM. Botulinum toxin type A for painful temporomandibular disorders: systematic review and meta-analysis. J Pain 2020 Mar–Apr; 21(3-4):281–293. https://doi.org/10.1016/j.jpain.2019.08.011. Epub 2019 Sep 9. PMID: 31513934.

Chapter 11
Botulinum Neurotoxins for Relief of Pain Associated with Spasticity

Introduction

Spasticity is a clinical condition caused by damage to the central nervous system (brain or spinal cord) and characterized by a velocity-dependent increase in stretch reflex (muscle tone) in the absence of volitional activity [1]. Many affected patients also demonstrate pathological reflexes and signs (Babinki, Wartenberg) indicating CNS damage. Spasticity occurs in 38% of patients with stroke [2], half of patients with spinal cord injury [3], and one-third of patients with brain injury [4]. Rizzo et al. [5] found mild to severe spasticity (19% mild, 17% moderate, 13% severe) in 49% of 513 patients surveyed from North American registry for multiple sclerosis. In one-third of the group, impairment of quality of life could be attributed to spasticity. Lower limb spasticity has been reported in one-third of adults after stroke, half to two-thirds of patients with multiple sclerosis, and three-quarters of children with cerebral palsy [6].

Increased tone and stiffness of muscles in spasticity limits and slows limb movements and, when present in the lower limbs, interrupts ambulation. Progressive spasticity causes muscle shortening and contractures with loss of muscle contraction-relaxation mechanism and further limitation of movements. Treatment is aimed at reducing muscle tone, preventing complications, and alleviating pain. The incidence of pain in spasticity has not been sufficiently investigated. In some patients, spasticity-related pain (SRP) is quite severe and may become more disabling than the spasticity itself.

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_11

Pathophysiology of Spasticity and Spasticity Related Pain (SRP)

The pathophysiology of spasticity has been reviewed in a comprehensive two-part article by Jean-Michael Gracies [7, 8]. In brief, damage to the central nervous system leads to acute and chronic changes. The acute effects include paresis and short-term immobilization, whereas chronic effects include plastic rearrangements in the CNS as a result of either CNS injury and/or chronic disuse (Fig. 11.1). These changes influence the innervation of the muscles and the reflex arch leading to spasticity, spastic dystonia, and spastic co-contractions. The end result is muscle shortening and contracture caused by chronic spasticity and muscle disuse.

The exact mechanism through which a state of muscle hyperactivity and spasticity develops after CNS injury is still unclear. As emphasized by Gracies [7], extensive sprouting and new synapse formation may play an important role in inducing overactive stretch reflex since the new connections are often hyperexcitable and may act differently from those lost secondary to the CNS damage [9]. There is some evidence for both decreased reciprocal Ia inhibition (which inhibits alpha motor neurons via a disynaptic interneuron) and decreased Ib, non-reciprocal inhibition (which via activity of Golgi tendons limits limb extension), suggesting contributions from these mechanisms to the increased stretch reflexes in spasticity [10]. Furthermore, muscle immobility (as seen in spastic paresis), increases the discharge of muscle spindles [11] which via the gamma system can lead to increased stretch reflexes and increased muscle tone. Finally, electrophysiological studies of patients with spastic hemiplegia indicate hyperexcitability of small group II afferents (originating from muscle spindle's secondary endings) which in a normal state inhibit motor neurons via spinal interneurons [12]. The function of these type II afferents is

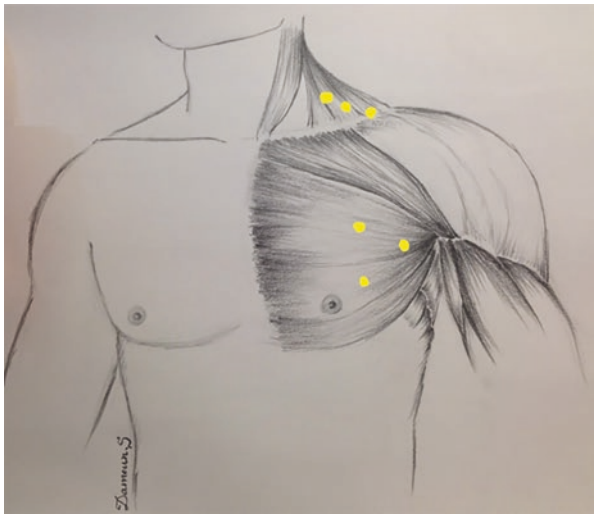

Fig. 11.1 The site of onabotulinumtoxinA (Botox) injections in case 11–1. (Drawing courtesy of Damoun Safarpour MD)

modulated and inhibited by descending rubro- and vestibulo-spinal pathways that often get damaged in CNS injuries.

On the other hand, Renshaw cell inhibition (RCI) and direct alpha motor neuron hyperexitability do not seem to play a major role in spasticity. In fact, in human, RCI has been shown to increase after CNS damage and in the presence of spasticity [13].

The pain associated with spasticity could be musculoskeletal directly related to spasticity and/or neuropathic as a result of the causative factor (e.g., spinal cord injury) [14]. Several mechanisms may cause musculoskeletal pain in spasticity. Some spasticity-related pain (SRP) occurs in the form of muscle spasms caused by increased muscle tone and enhanced reflex activity. Alternatively, the pain could arise from the affected joints that are limited in movement by the attached stiff, spastic muscles. The frequent pain from spastic muscles and painful joints can also set in motion spinal and supraspinal circuits which cause central sensitization leading to pain chronicity (Chap. 2). In small children, adductor spasticity could lead to hip subluxation and pain [15].

Treatment of Spasticity

Treatment of spasticity includes pharmacological and nonpharmacological approaches. Often the two are used to complement each other.

Nonpharmacological Treatment of Spasticity

As a noninvasive approach, physiotherapy is widely used for treatment of spasticity. It is generally believed that physiotherapy strengthens antagonist muscle groups and reduces muscle overactivity helping to prevent muscle shortening. The commonly used techniques used in physiotherapy include stretching, direct tendon pressure, heat and cold application, electrical stimulation, vibration, and casting. Although commonly used and believed to be helpful, high-quality studies evaluating the efficacy of physiotherapy in large cohorts of patients with spasticity are not available.

Pharmacological Therapy

Pharmacological agents, through different mechanisms, reduce the tone of muscles and improve spasticity. The commonly used drugs for treatment of spasticity include gabaergic agents, such as baclofen and benzodiazepines. Tizanidine, an alpha adrenergic drug, is also used widely [16–22]. Unfortunately, severe spasticity often requires larger doses of these medications that are beset by emergence of

undesirable side effects (sedation, hypotension). Severe and advanced cases of spasticity (especially in the lower limb) may require baclofen pump placement. Although treatment of spasticity may alleviate the associated pain, in most cases, pain relief requires addition of analgesic medications. The commonly used pharmacological agents used for associated pain include tricyclic antidepressants, nonsteroidal anti-inflammatory agents, and, in severe cases, opioid analgesics.

Procedural Approaches and Surgical Interventions

Electropuncture, transcranial, and trans-spinal stimulations have produced positive results in small clinical trials. Recently, several small, randomized clinical trials have shown the efficacy of extracorporeal shock wave therapy (ESWT) in spasticity. The mechanism through which applying shock waves to the muscle reduces spasticity still needs to be elucidated [23].

Selective dorsal rhizotomy is reserved for those patients with spasticity who do not respond to conventional pharmacological treatment. In children with cerebral palsy, selective dorsal rhizotomy can prevent hip dislocation by reducing severe spasticity [24–26].

Botulinum Toxin Studies in Spasticity That Have Included Assessment of Pain

This section covers the randomized, double-blind, placebo-controlled studies that have specifically assessed pain in adults' upper and lower limb spasticity and spasticity-related pain of children with or without cerebral palsy. The relevant literature was searched through Medline up to October 1st 2021. The results are summarized in tables and commented on in the conclusion paragraph of each section.

Upper Limb Spasticity-Related Pain in Adults

During the past 15 years, publication of research data from multicenter trials of BoNTs led to approval of ona, abo, and incobotulinumtoxinA (Botox, Dysport, Xeomin) by FDA for treatment of spasticity [27] [Table 11.1].

More recent studies provided data on duration of response to botulinum toxin therapy, sustainability of response with repeated injections, as well as effects of early versus late treatment in spasticity [28–30]. Real-life/real-world studies in a sizeable number of patients also supported the positive results of botulinum toxin therapy in spasticity concurring with the data from blinded studies [31].

Table 11.1 Clinical indications approved by FDA for botulinum toxins marketed in the United States

Generic and trade names	Abbreviation	Manufacturer	Approved indication (FDA)	Year of FDA approval
OnabotulinumtoxinA; Botox	OnaBoNT-A	Allergan -Inc; Dublin, Ireland	Upper limb spasticity;	2011 2017
			Adult lower limb spasticity; Pediatric upper limb spasticity	2019
IncobotulinumtoxinA; Xeomin	incoBoNT-A	Merz pharma GmbH & co; Frankfurt, Germany	Adult upper limb spasticity;	2015
			Children upper limb spasticity	2020
AbobotulinumtoxinA; Dysport	aboBoNT-A	Ipsen pharmaceutical; UK	Adult upper limb spasticity; Pediatric lower limb spasticity;	2015 2017
			Adult lower limb spasticity	2019

Meta-analysis of data provided by blinded studies also support the efficacy of different BoNTs in treatment of spasticity, as well as improvement of the patients' quality of life [32, 33]. In general, BoNT therapy in spasticity is safe, and serious side effects for onabotulinumtoxinA and incobotulinumtoxinA—even at doses as high as high 800–1200 units per session—are rare [34, 35]. In a large study which assessed incidence of bleeding in 1138 patients on antithrombotic therapy who had received BoNT injections, the incidence of bleeding was not higher than those patients who did not receive antithrombotic therapy (0.9% vs. 1.4%) [36].

The incidence of pain associated with upper limb spasticity still remains to be elucidated. In one study, 38.1% of 42 patients with upper limb spasticity complained of associated pain. The pain is often musculoskeletal in type, but depending on the pathology, some patients may experience neuropathic pain [37].

Eleven double-blinded, placebo-controlled studies of upper limb spasticity included pain assessment in their investigational design and reported the effect of BoNT therapy on spasticity-associated pain [38–48] [Table 11.2]. As can be seen in Table 11.2, studies that included assessment of pain used different pain scales. Five of 11 studies assessed pain via visual analogue scale (VAS). Two studies assessed pain via a subscale of disability assessment scale (DAS). This is a 0 to 4 scale that has pain as one of its four subscales (mobility, posture, dressing, pain). One study used McGill pain questionnaire short form (MGPQSF). The other three studies assed pain either by 0–3 or 0–5 scale.

Table 11.2 Double blind, placebo-controlled studies of BoNT's effects on upper limb spasticity that reported on BoNT's effect on spasticity-associated pain

Author, year	#Pts	Study class	Toxin	Dose units	Pain scale	Result	Comment
Bakheit et al., 2001 [38]	59	I	aboA	1000	0–3	No improvement	Pain scale, not standard
Childers et al., 2004 [39]	91	I	onaA	90, 180, 360	0–5	No improvement	Pain scale, not standard
Suputtitada et al., 2005 [40]	50	I	aboA	375, 500, 1000	Pain scale	Significant improvement	
Marco et al., 2007 [41]	31	I	aboA	500	VAS	Pain improved ($P = 0.001$) at 1, 2, 3, 4 months post-injection	
Yelnik Et al., 2007 [42]	20	II	aboA	500	VAS	Pain improved ($P = 0.025$) at 4 weeks post-injection	
Shaw et al., 2011 [43]	353	I	aboA	100, 200	VAS	Pain relief at 12 months post-injection ($P = 0.002$), but not at 1 & 3 months	
Rosales et al., 2012 [44]	163	I	aboA	500	VAS	Pain reduction ($P < 0.05$) at 4 and 24 weeks, post-injection	
Lam et al., 2012 [45]	55	I	aboA	1000	0–5	No improvement	Pain scale, not standard
Marciniak et al., 2012 [46]	37	I	onaA	140, 200	MPQSF	No improvement	
Elovic et al., 2016 [47]	465	I	incoA	400	DAS	Significant improvement, 42% versus 28% placebo ($P = 0.0007$)	
Abo et al., 2020 [48]	131	I	onaA	400, 250	DAS	In both toxin groups DAS slightly decreased compared to placebo	

onaA onabotulinumtoxinA(Botox), *aboA* abobotulinumtoxinA (Dysport), *rimaB* rimabotulinumtoxinB (Myobloc), *VAS* Visual analogue scale, *MGPQSF* McGill Pain questionnaire short form, *DAS* disability assessment scale (0–4 scale including four subscales, one being pain)

Comment

All four studies that used VAS as pain efficacy assessment reported efficacy of abobotulinumtoxinA in alleviating spasticity-associated pain. Using the efficacy assessment criteria of the American Academy of Neurology [49, 50], the level of evidence for efficacy for aboA in spasticity-related pain of upper limb (using VAS for pain assessment) is A (established efficacy) based on the availability of two or more class I studies. The delayed efficacy (at 12 months, probably after third injection) in the study of Shaw et al. [43], [Table 11.1] might be related to the small dose of aboA

used by the investigators (100 and 200 units vs. 500 and 1000 units used by others) and emergence of a better response after repeated injections. Such better late effect after repeat injections has been reported in other pain indications after BoNT treatment, especially with onaA administration in chronic migraine [51]. The efficacy of aboA in relieving spasticity-related pain is supported by a large prospective, open label European study [52] of 408 patients in which 58.9% of the patients reported pain relief. Evaluation of the efficacy of the other forms of botulinum neurotoxin in spasticity-related pain deserves further investigation via placebo-controlled studies.

Case 11–1

A 65-year-old gentleman had suffered an acute cerebral infarct and left hemiparesis three years earlier. The left-sided weakness gradually improved with physical therapy and regular exercise. He visited Yale Botulinum Toxin Treatment Clinic for evaluation and management of spasm and pain in the left pectoralis major and left trapezius muscles. The pain was constant for the past six months, but also occurred in the form of intermittent spasms. The pain interfered with his sleep and daily activities.

On examination, the left shoulder was elevated, and the left trapezius muscle demonstrated increased tone. The left pectoralis major muscle was also spastic, and its increased tone at rest caused overadduction of the left arm. Under electromyographic guidance, 120 units of onabotulinumtoxinA were injected into the trapezius and pectoralis muscles—each muscle received 20 units at three sites for a total of 60 units (Fig. 11.1). After one week, the patient reported cessation of spasms and marked improvement of daily discomfort. Repeat injections every three months remained effective post initiation of injection therapy during a close follow-up period of four years.

On the Patient Global Impression of Change scale (PGIC), a 1–7 scale (7 being very satisfactory), patient-rated his response to BoNT therapy as 7. There were no side effects after abobotulinumtoxinA injection. In particular, the injected dose caused no demonstrable weakness.

Lower Limb Spasticity-Related Pain of Adults

Pain assessment after BoNT injection has been ignored in several large studies of adult cohorts with lower limb spasticity [53–55]. Several open label and observational reports described improvement of spasticity-associated pain after BoNT injection into the lower limb muscles [56–59]. We found only five double-blind, placebo-controlled studies [60–63] that specifically included pain assessment and results after BoNTs treatment of lower limb spasticity (Table 11.3).

Table 11.3 Double-blind, placebo-controlled studies that included pain assessment and reported the results in patients with lower limb spasticity

Authors and date	Study class	# pts	Toxin	Dose	Scale	Result	Comment
Hayman et al., 2000 [60]	I	74	aboA	500, 1000, 1500	Frequency of spasms	Frequency improved in all groups. No difference between three doses	No statistical values provided
Pittock et al., 2003 [61]	I	233	aboA	500, 1000	0–3 scale	1000 units group: Pain relief at 4,8 and, 12 weeks ($P < 0.005$); 500 units group: Pain relief at 4 weeks $P < 0.005$)	Dose- dependent, longer response.
Gusev et al., 2008 [62]	II	55	aboA	500–750	VAS	Significant pain reduction in BoNT group ($P < 0.05$)	
Dunne et al., 2012 [63]	I	85	onaA	100, 200	VAS and spasm frequency	Both VAS and spasm frequency improved ($P = 0.02$ and 0.01, respectively)	
Wein et al., 2017 [64]	I	468	onaA	300	VAS	No pain relief during blinded phase	Pain improved during open label phase over three cycles

AboA abobotulinnumtoxinA (Dysport), *OnaA* onabotulinumtoxinA (Botox), *VAS* Visual analogue scale

Hyman et al. [60] studied 74 patients with lower limb spasticity stratified into four groups: placebo group and three groups receiving aboA with doses of 500, 1000, and 1500 units, respectively. The frequency of muscle spasms was assessed among secondary outcomes. The authors reported that after aboA injection, the frequency of muscle spasms improved in all three groups that received different doses of aboA. The difference between the groups as to the magnitude of pain relief was not significant.

Another group of investigators [61] used the same study design assessing efficacy of aboA in calf spasticity after stroke. The study encompassed a much larger group of patients (234 from 19 centers), stratified into four groups of placebo and aboA toxin (500, 1000, and 1500 units). Injections were made at four points into the gastrocnemius muscle. The authors used a 0–3 scale for severity of pain. No pain relief was seen in the placebo group. All three aboA groups reported significant pain relief which was more notable at 8 weeks with 1000 units ($P = 0.0019$) and 1500 units ($P = 0.0066$), but also at four weeks ($P = 0.0044$ and $P = 0.0040$, respectively) and 12 weeks ($P = 0.0128$ and $P = 0.0488$, respectively). A lower level of pain relief was noted at eight weeks in the group receiving 500 units ($P = 0.0222$).

Gusev et al. [62] studied the effect of aboA injections units into the adductor muscles of each leg in 55 patients with multiple sclerosis. The toxin dose varied from 500 to 750 units depending on the severity of spasticity and the patient's weight. Patients in the toxin group demonstrated significant pain relief compared to the placebo group ($P < 0.05$).

Dunne et al. [63] investigated the efficacy of onabotulinumtoxinA in 85 patients (multicenter study) with painful plantar flexor/invertor spasticity after stroke. The frequency of painful spasms was assessed before and after treatment. Three study groups were designed to receive saline, 100 or 200 units of onabotulinumtoxinA. The onabotulinumtoxinA-injected subjects showed significant reduction of spasm frequency (22/54 vs. 4/29, $P = 0.01$), pain reduction (8/54 versus 1/29, $P = 0.02$), and increased active dorsiflexion (8/54 versus 1/29 $P = 0.03$).

Wein et al. [64] conducted a randomized, blinded study on 463 patients with lower limb spasticity. The blinded arm of the study lasted for 12 weeks and then was followed by an open label arm for 48 weeks covering three cycles of injections. Pain was assessed as a secondary outcome by visual analogue scale (VAS). Toxin (onaA) injections were performed into plantar flexors of the foot (gastrocnemius and soleus). The injection dose paradigm was flexible using 100–300 units (majority of patients received 300 units). The authors noted no significant pain relief at the primary evaluation point (6 weeks) of the blinded arm of the study. However, patients reported pain relief during all three cycles of the study's open label arm over the following 48 weeks.

Case 2

A 42-year-old man with 16 years history of remitting/relapsing multiple sclerosis complained of stiffness and pain in his left big toe. The toe became gradually dorsiflexed and would not fit easily in the shoe. Physiotherapy slightly helped, but the problem persisted and interfered with his quality of life. The patient was injected with 100 units of onaA at two points (50/point) into the left extensor hallucis longus under EMG guidance [Fig. 11.2]. Two weeks following onaA injection, he reported significant pain relief and loss of toe stiffness. He was followed with good results from quarterly injections in the Yale Botulinu Toxin Clinic for four years.

Comment

Information from blinded studies on the effects of BoNT therapy on spasticity-related pain in the lower limbs of adults is limited. Using the efficacy criteria of the American Academy of Neurology [51, 52], a level B efficacy (probably effective) can be given to aboA based on availability of one class I study [61]. The same efficacy rating applies to onaA (one class I study), Dunne et al. 2012 [63]). The study

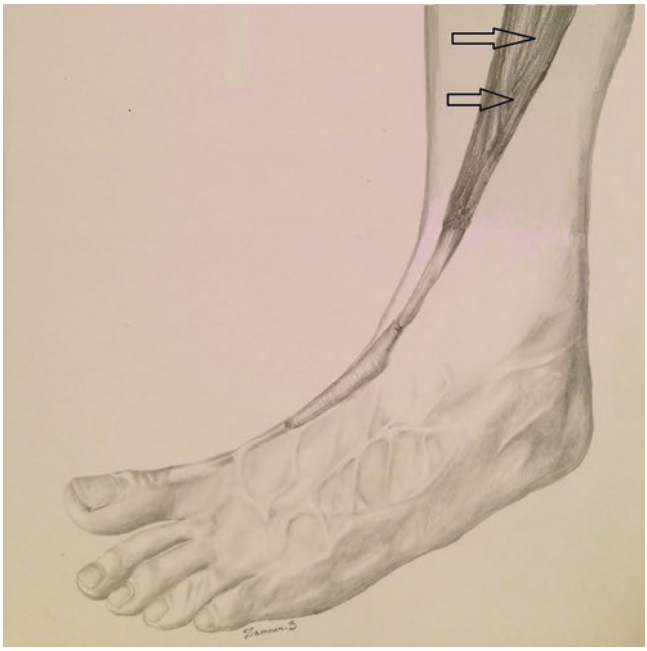

Fig. 11.2 The site of injections in patient 2. (Drawing courtesy of Damoun Safarpour, MD)

of Hyman et al. [60] is hard to interpret due to the fact that both the placebo and toxin improved pain significantly. Such finding implies a large placebo effect and does not allow proper efficacy assessment. In the study of Wein et al. [64], although the patients blinded arm of the study did not show pain relief, during the open arm of the study, pain relief after onaA injection was noted over all three cycles.

Effects of BoNT Treatment on Pain of Children with Cerebral Palsy and Spasticity

Cerebral palsy (CP) is characterized by a heterogeneous group of muscle and posture disorders often caused by anoxic and traumatic brain damage that had occurred during the first two years of life. The incidence of cerebral palsy is 2/1000 live births worldwide [65]. Majority of the children affected by CP develop spasticity over time. Approximately 76% of young adults with cerebral palsy complain of chronic pain [66]. Spasticity and pain often co-exist in cerebral palsy. Untreated spasticity can lead to muscle contracture and fixed limb posture that can also enhance pain.

Several open label and observational studies have reported reduction of pain frequency and intensity after BoNT treatment in children with cerebral palsy [67–71].

In a study of 26 children with CP, spasticity, and hip pain [68], investigators injected either onaA (9 children) or aboA (17 childern) into adductor magnus, hamstring, and ileopsoas muscles. The dose per session was up to 12 units/kg of body weight for onaA and up to 30 units/kg for aboA. The pain was measured by pediatric pain profile. Injection of both neurotoxins resulted in marked reduction of pain at three months ($P = 0.001$).

Rivard et al. [69] asked the parents of 34 children with CP (mean age 9) and spasticity-related pain about the intensity and frequency of pain after BoNT-A injection into spastic muscle. The parents reported cessation of pain at week 4 in 62% of the children.

A multicenter, prospective, observational study from France [70] reported on treatment of 286 children suffering from CP with botulinumtoxinA, followed for 12 months. Administration of botulinumtoxinA improved range of motion, movement capacity, gait, and spasticity-related pain.

In very young children, cerebral palsy with bilateral proximal lower limb spasticity often causes hip dislocation resulting in significant pain, impaired ambulation, and disability. In a study of 98 children, Pascal-Leone from La Paz hospital in Mardid [71] found continuous worsening of lateral hip migration in 86% and full subluxation in 11.4%. Administration of BoNT into hip adductor and iliopsoas muscles stopped the progression in 74% of the children via reduced spasticity and reverted the condition in another 14%. The author advocates early and aggressive treatment, every three to four months to prevent this complication.

Blinded studies are difficult to perform in small children. Only a few blinded studies of BoNT effect in cerebral palsy included pain assessment and reported the results (Table 11.4).

In the year 2000, Barnwood et al. reported on the results of a prospective, randomized, double-blind study in 16 children with CP and spasticity who were undergoing adductor release procedure [72]. The children were diplegic or quadriplegic with a mean age of 4.7 years. The surgery was performed in order to prevent hip subluxation. The authors used onabotulinumtoxinA (onaA), Allergan Inc., prepared as 10 units/0.1 cc (100 unit vial diluted with 1 cc saline). Each adductor muscle was injected at two sites (2 units/kg per site) for a total dose of 8 units/kg, 5 to 10 days before surgery. The patients in the onaA group did considerably better in respect to postoperative care, reduction of analgesic requirement, and shortening the length of hospital stay. The mean pain score in the onaA group showed a reduction of 74% ($P < 0.003$), and patients' analgesic requirement dropped approximately by 50% ($P < 0.005$). The onaA group also had significantly shorter length of hospital stay with 33% reduction in length of stay ($P < 0.003$).

Copeland et al. [73] studied 41 nonambulatory children with advanced spasticity and cerebral palsy. The study was prospective and double-blind. The mean age of the children was 7.1 years. Twenty-three children received BoNT-A and 18 received a sham procedure. The efficacy of injections was assessed during a 12-month follow-up period by physicians using a Modified Ashworth Scale, joint range of

Table 11.4 Double-blind placebo-controlled studies of botulinum neurotoxin effects in cerebral palsy that included assessment of pain

Authors and year	# pts	Class	Toxin	Dose units	Pain scale	Results	Comment
Barwood et al., 2000 [72]	16	II	onaA	8u/kg	0–9	Reduction of mean pain score (74%) ($P < 0.003$); 50% reduction of mean analgesic requirement ($P < 0.005$)	
Copeland et al. 2013 [73]	31	II	onaA	400 12u/kg	VAS	Significant pain reduction in the toxin group at 4 and 12 weeks (P values<0.05 and < 0.01, respectively)	
Jacobson et al., 2021 [74]	16 8 in each Group	II	aboA	1500 Adults with CP	VAS <2 or more grades	Both toxin and placebo improved pain. At week 10, toxin group showed a trend for significance (Fig. 11.3)	Small number of patients, study stopped mid-way

motion, Physician Rating Scale, Gillette Functional Assessment Questionnaire, and Gross Motor Function Measure-66, by patients/parents (Visual Analogue Scale) and the pediatric pain profile (PPP). OnabotulinumtoxinA was injected into spastic muscles using a maximum dose of 12 units/kg or a total dose of 400 units per session. Following administration of onaA, in addition to improvement of the aforementioned parameters, the children who received BoNT injections (and/or parents) reported significant reduction of pain compared to baseline at 4 and 16 weeks (P values <0.05 and < 0.01, respectively). In the sham procedure group, no significant response was observed.

Jacobson et al. [74] have studied the effect of 1500 units of abobotulinumtoxinA on pain of 16 patients with adults who suffered from cerebral palsy and spasticity. The study was double- blind and parallel design including eight patients in each group (toxin and placebo). The pain response to the toxin and placebo was assessed via VAS. At six weeks (primary outcome time- point), there was no significant difference between toxin and placebo groups (five responded to placebo, four to toxin). At 10 weeks, however, there was a trend of response (approximately two grade reduction in VAS) for the toxin group (Fig. 11.3).

In collaboration with our pediatric neurologist, Mark Difazio M.D., during the years 1994–2004, we treated and followed over 200 children with cerebral palsy with onabotulinumtoxinA at Walter Reed Army Medical Center, Washington DC. Some of the children were followed up to eight years. The maximum dose used per session was 12 units/kg. Injections (upper or lower limb) were effective in reducing spasticity, improving quality of life (sleep, hygiene, mood, irritability), and reducing pain. In general, parents were very satisfied with the results. No serious side effects were noted with the applied doses and after repeated injections. My continued experience with treatment of child spasticity with onabotulinumtoxinA at

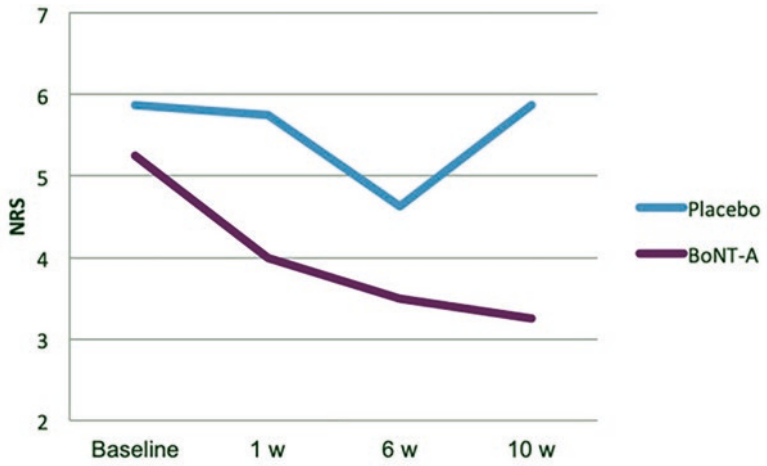

Fig. 11.3 Ten weeks after initiation of botulinumtoxin treatment, the toxin group demonstrates approximately two grade pain reduction in VAS. (Jacobson et al. 2021 [74]. From Frontiers of Neurology. Courtesy of PMC publisher)

Yale Botulinum Toxin Clinic (years 2004–2015) agrees with my practice in the Washington D.C area. The parent satisfaction at Yale was similar to that of Walter Reed Medical Center in Washington.

Comment

Conduction of double-blind studies for assessing the efficacy of BoNTs on spasticity-related pain in children with cerebral palsy is difficult due to procedural and ethical issues. Moreover, assessing the effect of toxin on pain is difficult, especially in small children. Of the three studies cited in Table 11.4, the result of one study [74] is hard to interpret due to a high placebo effect that makes efficacy assessment invalid. Based on the other two blinded studies [72, 73], both class II, the level of efficacy for onabotulinumtoxinA in spasticity-associated pain in CP can be considered B (probably effective) based on two class II studies [49, 50].

Determination of a safe dose and safe ceiling (dose/day) has been the focus of research in pediatric application of toxin therapy for the past two decades. Investigators of the United States usually do not exceed 16–20 units/kg (in case of onaA) in the studies of cerebral palsy. European guideline of 2009 recommended the use of higher doses in children [75]. Depending on the child's weight, up to 400–600 units of onaA (20–30 units/Kg) and 1000 units (20–30 units/ Kg of aboA) were recommended [76]. The recent reviews (based on mostly lower doses used in the United States) including meta-analysis of the published data in pediatric literature indicate that BoNT therapy in cerebral palsy is safe and side effects, in general,

are mild and tolerable [77–80]. Recently, Almina et al. [81] reviewed the literature on the analgesic role of BoNTs in pain associated with cerebral palsy and advocated the need for high-quality studies in this area.

Can early injection of botulinum toxin into the spastic muscles of children with cerebral palsy prevent the development of contracture that enhances the existing pain? Cosgrove and Graham [82] have shown that in mice with hereditary spastic paraplegia, early injection of onabotulinummtoxinA into the spastic muscles allows the muscles to grow within 2% of mature muscles. In the noninjected mice, the mature muscles were 16% smaller, a difference that was highly significant. Recently, Lindsay et al. [83] studied the effect of injecting onaA into the muscles of 91 adults soon after stroke in a double-blinded, placebo-controlled study. Contracture formation was slower in the treatment group. BoNTA reduced the need for concomitant contracture treatment and did not interfere with the recovery of arm function.

The Mechanism of Action of BoNTs in Spasticity-Related Pain (SRP)

The mode of action of BoNTs in SRP most probably involves both muscular and neural mechanisms. On the muscular side, BoNTs block the release of acetylcholine from presynaptic vesicles causing muscle relaxation that, in turn, can reduce the frequency of painful spasms. Furthermore, relaxation of muscles leads to better joint motility and prevents secondary pain and discomfort related to awkward joint–muscle interactions. In children, focused relaxation of hip adductors can prevent subluxation and related discomfort. On the neural side, some of the pain in advanced spasticity and contracture may originate from peripheral nerve fibers in the affected contracted tissue. Numerous animal studies have shown that BoNTs inhibit the release of pain mediators (glutamate, substance P, and calcitonin gene peptide) from peripheral nerve endings and dorsal root ganglia (Chap. 2).

Also, it is now increasingly recognized that peripheral injection of BoNTs (intramuscular or subcutaneous) has a direct central effect via retrograde transport and transcytosis (Mazzocchio and Caleo, 2014). In support of the central effect of the toxin, Bach-Rojecky et al. (2010) have shown bilateral improvement of leg hyperalgesia after unilateral injection of onabotulinumtoxinA into the affected area on one side. Furthermore, following injection of the toxin into the rat's eye, truncated SNAP-25 was detected in the midbrain tectum terminals despite the Wallerian degeneration of the axon that transports the toxin (Restani et al., 2012).

Such central effects can invariably impact the function of spinal circuits, interneurons, and spinal sensory neurons, all of which play an important role in spasticity and spasticity-related pain.

Conclusion

Blinded and placebo-controlled studies of adult spasticity have illustrated the efficacy of abobotulinum toxinA in management of upper limb spasticity-related pain. In lower limb spasticity-related pain, however, data is still limited though it strongly suggests efficacy. Studies in children with cerebral palsy suggest efficacy of different types of BoNTs in reducing spasticity-related pain. BoNT injection into spastic hip adductor muscles of children with CP may be helpful in preventing the painful and serious complication of hip subluxation.

References

1. Lance JW. What is spasticity? Lancet. 1990;335(8689):606. https://doi.org/10.1016/0140-6736(90)90389-m.
2. Watkins CL, Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK. Prevalence of spasticity post stroke. Clin Rehabil. 2002;16:515–22.
3. Wedekind C, Lippert-Grüner M. Long-term outcome in severe traumatic brain injury is significantly influenced by brainstem involvement. Brain Inj. 2005;19:681–4.
4. Noreau L, Proulx P, Gagnon L, Drolet M, Laramée MT. Secondary impairments after spinal cord injury: a population-based study. Am J Phys Med Rehabil. 2000;79:526–35.
5. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler. 2004;10:589–95.
6. Martin A, Abogunrin S, Kurth H, Dinet J. Epidemiological, humanistic, and economic burden of illness of lower limb spasticity in adults: a systematic review. Neuropsychiatr Dis Treat. 2014;10:111–22.
7. Gracies JM. Pathophysiology of spastic paresis. I: paresis and soft tissue changes. Muscle Nerve. 2005;31:535–51.
8. Gracies JM. Pathophysiology of spastic paresis. II: emergence of muscle overactivity. Muscle Nerve. 2005;31:552–71.
9. Gioux M, Petit J. Effects of immobilizing the cat peroneus longus muscle on the activity of its own spindles. J Appl Physiol (1985). 1993;75(6):2629–35. PMID: 8125883 https://doi.org/10.1152/jappl.1993.75.6.2629.
10. Crone C, Johnsen LL, Biering-Sorensen F, Nielsen JB. Appearance of reciprocal facilitation of ankle extensors from ankle flexors in patients with stroke or spinal cord injury. Brain. 2003;126:495–507.
11. Williams RG. Sensitivity changes shown by spindle receptors in chronically immobilized skeletal muscle. J Physiol Lond. 1980;306:26–7.
12. Marque P, Simonetta-Moreau M, Maupas E, Roques CF. Facilitation of transmission in heteronymous group II pathways in spastic hemiplegic patients. J Neurol Neurosurg Psychiatry. 2001;70:36–42.
13. Katz R, Pierrot-Deseilligny E. Recurrent inhibition of alphamotor neuron in patients with upper motor neuron lesions. Brain. 1982;105:103–24.
14. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol. 2016;79(4):569–78. https://doi.org/10.1002/ana.24605. Epub 2016 Feb 16. PMID: 26814620; PMCID: PMC4825405.
15. Marcström A, Hägglund G, Alriksson-Schmidt AI. Hip pain in children with cerebral palsy: a population-based registry study of risk factors. BMC Musculoskelet Disord. 2019;20(1):62. https://doi.org/10.1186/s12891-019-2449-8. PMID: 30736784; PMCID: PMC6368700.

16. McClugage SG 3rd, Bauer DF. Review of tone management for the primary care provider. Pediatr Clin N Am 2021;68(4):929–944. https://doi.org/10.1016/j.pcl.2021.04.018. PMID: 34247718.
17. Reilly M, Liuzzo K, Blackmer AB. Pharmacological management of spasticity in children with cerebral palsy. J Pediatr Health Care 2020;34(5):495–509. https://doi.org/10.1016/j.pedhc.2020.04.010. PMID: 32861428.
18. Zhang B, Karri J, O'Brien K, DiTommaso C, Kothari S, Li S. Spasticity management in persons with disorders of consciousness. PM R 2021;13(7):657–665. https://doi.org/10.1002/pmrj.12458. Epub 2020 Aug 28. PMID: 32716119.
19. Kim H, Stanford R. Facts and de facto treatment of spasticity. J Pediatr Rehabil Med. 2020;13(2):189–93. https://doi.org/10.3233/PRM-200737. PMID: 32568127
20. Enslin JMN, Rohlwink UK, Figaji A. Management of spasticity after traumatic brain injury in children. Front Neurol. 2020;11:126. https://doi.org/10.3389/fneur.2020.00126. PMID: 32153498; PMCID: PMC7047214.
21. Dy R, Roge D. Medical updates in management of hypertonia. Phys Med Rehabil Clin N Am 2020;31(1):57–68. https://doi.org/10.1016/j.pmr.2019.09.010. PMID: 31760994.
22. Milligan J, Ryan K, Lee J. Demystifying spasticity in primary care. Can Fam Physician. 2019;65(10):697–703. PMID: 31604736; PMCID: PMC6788672.
23. Jia G, Ma J, Wang S, Wu D, Tan B, Yin Y, Jia L, Cheng L. Long-term effects of extracorporeal shock wave therapy on Poststroke spasticity: a meta-analysis of randomized controlled trials. J Stroke Cerebrovasc Dis 2020;29(3):104591. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104591. Epub 2019 Dec 31. PMID: 31899073.
24. Patel R, Rhee PC. Team approach: multidisciplinary perioperative care in upper-extremity reconstruction for adults with spasticity and contractures. JBJS Rev 2020;8(4):e0164. https://doi.org/10.2106/JBJS.RVW.19.00164. PMID: 32304496.
25. Tu A, Steinbok P. Long term outcome of selective dorsal Rhizotomy for the management of childhood spasticity-functional improvement and complications. Childs Nerv Syst. 2020;36(9):1985–94. https://doi.org/10.1007/s00381-020-04747-8. Epub 2020 Jun 23. PMID: 32577879
26. Agrawal M, Samala R, Doddamani R, Agrawal D, Chandra SP. The role of selective dorsal rhizotomy in the management of post-traumatic spasticity: systematic review. Neurosurg Rev. 2021;44(1):213–21. https://doi.org/10.1007/s10143-020-01255-w. Epub 2020 Feb 5. PMID: 32020384
27. Brown EA, Schütz SG, Simpson DM. Botulinum toxin for neuropathic pain and spasticity: an overview. Pain Manag. 2014;4:129–51.
28. Gracies JM, O'Dell M, Vecchio M, Hedera P, Kocer S, Rudzinska-Bar M, Rubin B, Timerbaeva SL, Lusakowska A, Boyer FC, Grandoulier AS, Vilain C, Picaut P; International abobotulinumtoxinA adult upper limb spasticity study group. Effects of repeated abobotulinumtoxinA injections in upper limb spasticity. Muscle Nerve. 2018;57(2):245–254. https://doi.org/10.1002/mus.25721. Epub 2017 Aug 13. PMID: 28590525; PMCID: PMC5811783.
29. Field M, Splevins A, Picaut P, van der Schans M, Langenberg J, Noort D, Snyder D, Foster K. Correction: Field, M et al. AbobotulinumtoxinA (Dysport®), OnabotulinumtoxinA (Botox®), and IncobotulinumtoxinA (Xeomin®) neurotoxin content and potential implications for duration of response in patients. Toxins (Basel). 2019;11(2):115. https://doi.org/10.3390/toxins11020115. Erratum for: Toxins (Basel). 2018 Dec 13;10(12): PMID: 30781899; PMCID: PMC6410060.
30. Wissel J, Fheodoroff K, Hoonhorst M, Müngersdorf M, Gallien P, Meier N, Hamacher J, Hefter H, Maisonobe P, Koch M. Effectiveness of abobotulinumtoxinA in post-stroke upper limb spasticity in relation to timing of treatment. Front Neurol. 2020;11:104. https://doi.org/10.3389/fneur.2020.00104. PMID: 32184753; PMCID: PMC7058702.
31. Sarzyńska-Długosz I, Szczepańska-Szerej A, Drużdż A, Łukomski T, Ochudło S, Fabian A, Sobolewski P, Mariańska K, Maciejewska J, Mulek E, Niedzielska A, Raymond R, Brzózka MM, Jessa-Jabłońska M. Real-world effectiveness of abobotulinumtoxinA (Dysport®) in

adults with upper limb spasticity in routine clinical practice: an observational study. Neurol Neurochir Pol. 2020;54(1):90–9. https://doi.org/10.5603/PJNNS.a2020.0004. Epub 2020 Jan 20. PMID: 31956971
32. Xie HM, Guo TT, Sun X, Ge HX, Chen XD, Zhao KJ, Zhang LN. Effectiveness of botulinum Toxin a in treatment of hemiplegic shoulder pain: a systematic review and meta-analysis. Arch Phys Med Rehabil 2021;102(9):1775–1787. https://doi.org/10.1016/j.apmr.2020.12.010. Epub 2021 Jan 14. PMID: 33454279.
33. Sun LC, Chen R, Fu C, Chen Y, Wu Q, Chen R, Lin X, Luo S. Efficacy and safety of botulinum toxin type A for limb spasticity after stroke: A meta-analysis of randomized controlled trials. Biomed Res Int. 2019;2019:8329306. https://doi.org/10.1155/2019/8329306. PMID: 31080830; PMCID: PMC6475544.
34. Intiso D, Simone V, Bartolo M, Santamato A, Ranieri M, Gatta MT, Di Rienzo F. High dosage of botulinum toxin type A in adult subjects with spasticity following acquired central nervous system damage: where are we at? Toxins (Basel). 2020;12(5):315. https://doi.org/10.3390/toxins12050315. PMID: 32397674; PMCID: PMC7291232.
35. Dressler D, Saberi FA, Kollewe K, Schrader C. Safety aspects of incobotulinumtoxinA high-dose therapy. J Neural Transm (Vienna) 2015;122(2):327–333. https://doi.org/10.1007/s00702-014-1252-9. Epub 2014 Jul 17. PMID: 25030362.
36. Dimitrova R, James L, Liu C, Orejudos A, Yushmanova I, Brin MF. Safety of onabotulinumtoxinA with concomitant antithrombotic therapy in patients with muscle spasticity: A retrospective pooled analysis of randomized double-blind studies. CNS Drugs. 2020;34(4):433–445. https://doi.org/10.1007/s40263-020-00709-5. PMID: 32170665; PMCID: PMC7125063.
37. Rosales RL, Balcaitiene J, Berard H, Maisonobe P, Goh KJ, Kumthornthip W, Mazlan M, Latif LA, Delos Santos MMD, Chotiyarnwong C, Tanvijit P, Nuez O, Kong KH. Early abobotulinumtoxinA (Dysport®) in post-stroke adult upper limb spasticity: ONTIME Pilot Study. Toxins (Basel). 2018 Jun 21;10(7):253. https://doi.org/10.3390/toxins10070253. PMID: 29933562; PMCID: PMC6070912.
38. Bakheit AM, Pittock S, Moore AP, Wurker M, Otto S, Erbguth F, Coxon L. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type a in upper limb spasticity in patients with stroke. Eur J Neurol. 2001;8:559–65.
39. Childers MK, Brashear A, Jozefczyk P, Reding M, Alexander D, Good D, Walcott JM, Jenkins SW, Turkel C, Molloy PT. Dose-dependent response to intramuscular botulinum toxin type a for upper-limb spasticity in patients after a stroke. Arch Phys Med Rehabil. 2004;85:1063–9.
40. Suputtitada A, Suwanwela NC. The lowest effective dose of botulinumA toxin in adult patients with upper limb spasticity. Disabil Rehabil2005; 27:176–184.
41. Marco E, Duarte E, Vila J, Tejero M, Guillen A, Boza R, Escalada F, Espadaler JM. Is botulinum toxin type a effective in the treatment of spastic shoulder pain in patients after stroke? A double-blind randomized clinical trial. J Rehabil Med 2007 Jul;39(6):440–447. https://doi.org/10.2340/16501977-0066. PMID: 17624477.
42. Yelnik AP, Colle FM, Bonan IV, Vicaut E. Treatment of shoulder pain in spastic hemiplegia by reducing spasticity of the subscapular muscle: a randomised, double-blind, placebo-controlled study of botulinum toxin A. J Neurol Neurosurg Psychiatry. 2007 Aug;78(8):845–8. https://doi.org/10.1136/jnnp.2006.103341. Epub 2006 Nov 6. PMID: 17088333; PMCID: PMC2117719.
43. Shaw LC, Price CI, van Wijck FM, Shackley P, Steen N, Barnes MP, Ford GA. Botulinum Toxin for the upper limb after stroke (BoTULS) trial: effect on impairment, activity limitation, and pain. Stroke. 2011;42:1371–9.
44. Rosales RL, Kong KH, Goh KJ, Kumthornthip W, Mok VC, Delgado-De Los Santos MM, Chua KS, Abdullah SJ, Zakine B, Maisonobe P, Magis A, Wong KS. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke. A randomized controlled trial.Neurorehabil. Neural Repair. 2012;26:812–21.
45. Lam K, Lau KK, So KK, Tam CK, Wu YM, Cheung G, Liang KS, Yeung KM, Lam KY, Yui S, Leung C. Can botulinum toxin decrease carer burden in long term care residents with upper limb spasticity? A randomized controlled study. J Am Med Dir Assoc. 2012;13:477–84.

46. Marciniak CM, Harvey RL, Gagnon CM, Duraski SA, Denby FA, McCarty S, Bravi LA, Polo KM, Fierstein KM. Does botulinum toxin type a decrease pain and lessen disability in hemiplegic survivors of stroke with shoulder pain and spasticity?: a randomized, double-blind, placebo-controlled trial. Am J Phys Med Rehabil 2012 Dec;91(12):1007–1019. https://doi.org/10.1097/PHM.0b013e31826ecb02. PMID: 23064478.
47. Elovic EP, Munin MC, Kaňovský P, Hanschmann A, Hiersemenzel R, Marciniak C. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity. Muscle Nerve. 2016 Mar;53(3):415–21. https://doi.org/10.1002/mus.24776. Epub 2015 Dec 15. Erratum in: Muscle Nerve. 2016 Jun;54(1):170. PMID: 26201835; PMCID: PMC5064747.
48. Abo M, Shigematsu T, Hara H, Matsuda Y, Nimura A, Yamashita Y, Takahashi K. Efficacy and safety of onabotulinumtoxinA 400 units in patients with post-stroke upper limb spasticity: final report of a randomized, double-blind, placebo-controlled trial with an open-label extension phase. Toxins (Basel). 2020 Feb 18;12(2):127. https://doi.org/10.3390/toxins12020127. PMID: 32085529; PMCID: PMC7077183.
49. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology 2008 Nov 11;71(20):1639–1643. https://doi.org/10.1212/01.wnl.0000336535.27773.c0. PMID: 19001255.
50. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology 2008 Nov 11;71(20):1634–1638. https://doi.org/10.1212/01.wnl.0000336533.19610.1b. PMID: 19001254.
51. Aurora SK, Dodick DW, Diener HC, DeGryse RE, Turkel CC, Lipton RB, Silberstein SD. 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.
52. Jost WH, Hefter H, Reissig A, Kollewe K, Wissel J. Efficacy and safety of botulinum toxin type a (Dysport) for the treatment of post-stroke arm spasticity: results of the German-Austrian open-label post-marketing surveillance prospective study. J Neurol Sci. 2014;337:86–90.
53. Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M; GSK1358820 Spasticity Study Group. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. J Neurol. 2010 Aug;257(8):1330–7. https://doi.org/10.1007/s00415-010-5526-3. Epub 2010 Apr 1. Erratum in: J Neurol. 2010 Aug;257(8):1416. PMID: 20358216; PMCID:
54. Verplancke D, Snape S, Salisbury CF, Jones PW, Ward AB. A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury. Clin Rehabil 2005 Mar;19(2):117–25. https://doi.org/10.1191/0269215505cr827oa. PMID: 15759526.
55. Datta Gupta A, Visvanathan R, Cameron I, Koblar SA, Howell S, Wilson D. Efficacy of botulinum toxin in modifying spasticity to improve walking and quality of life in post-stroke lower limb spasticity - a randomized double-blind placebo controlled study. BMC Neurol. 2019 May 11;19(1):96. https://doi.org/10.1186/s12883-019-1325-3. PMID: 31078139; PMCID: PMC6511142. Gait improved.
56. De Icco R, Perrotta A, Berra E, Allena M, Alfonsi E, Tamburin S, Serrao M, Sandrini G, Tassorelli C. OnabotulinumtoxinA reduces temporal pain processing at spinal level in patients with lower limb spasticity. Toxins (Basel). 2019 Jun 20;11(6):359. https://doi.org/10.3390/toxins11060359. PMID: 31226803; PMCID: PMC6628414.
57. Esquenazi A, Bavikatte G, Bandari DS, Jost WH, Munin MC, Tang SFT, Largent J, Adams AM, Zuzek A, Francisco GE. Long-term observational results from the ASPIRE study: OnabotulinumtoxinA treatment for adult lower limb spasticity. PM R 2020 Nov 5. https://doi.org/10.1002/pmrj.12517. Epub ahead of print. PMID: 33151636.
58. López de Munain L, Valls-Solé J, Garcia Pascual I, Maisonobe P; on behalf of the VALGAS investigators group. Botulinum toxin type A improves function according to goal attainment in adults with poststroke lower limb spasticity in real life practice. Eur Neurol.

2019;82(1–3):1–8. https://doi.org/10.1159/000503172. Epub 2019 Nov 14. PMID: 31726452; PMCID: PMC7114896.
59. Santamato A, Micello MF, Panza F, Fortunato F, Pilotto A, Giustini A, Testa A. Safety and efficacy of incobotulinum toxin type a (NT 201-Xeomin) for the treatment of post-stroke lower limb spasticity: a prospective open-label study. Eur J Phys Rehabil Med. 2013;49:483–9.
60. Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreczy-Kleedorfer B, Poewe W, Wissel J, Bain P, Glickman S, Sayer A, Richardson A, Dott C. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomized, double blind, placebo controlled, dose ranging study. J Neurol Neurosurg Psychiatry. 2000;68:707–12.
61. Pittock SJ, Moore AP, Hardiman O, Ehler E, Kovac M, Bojakowski J, Al Khawaja I, Brozman M, Kanovský P, Skorometz A, Slawek J, Reichel G, Stenner A, Timerbaeva S, Stelmasiak Z, Zifko UA, Bhakta B, Coxon E. 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.
62. Gustav YI, Banach M, Simonow A, et al. Efficacy and safety of botulinum type a toxin in adductor spasticity due to multiple sclerosis. J Musculoskelet Pain. 2008;16:175–8.
63. Dunne JW, Gracies JM, Hayes M, Zeman B, Singer BJ, Multicentre Study Group. A prospective, multicentre, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat plantarflexor/invertor overactivity after stroke. Clin Rehabil. 2012;26:787–97.
64. Wein T, Esquenazi A, Jost WH, Ward AB, Pan G, Dimitrova R. OnabotulinumtoxinA for the treatment of poststroke distal lower limb spasticity: a randomized trial. PM R 2018 Jul;10(7):693–703. https://doi.org/10.1016/j.pmrj.2017.12.006. Epub 2018 Jan 9. PMID: 29330071.
65. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013;55:509–19. https://doi.org/10.1111/dmcn.12080.
66. McKinnon CT, Meehan EM, Harvey AR, Antolovich GC, Morgan PE. Prevalence and characteristics of pain in children and young adults with cerebral palsy: a systematic review. Dev Med Child Neurol. 2019;61:305–14. https://doi.org/10.1111/dmcn.14111.
67. Gooch JL, Sandell TV. Botulinum toxin for spasticity and athetosis in children with cerebral palsy. Arch Phys Med Rehabil 1996 May;77(5):508–11. https://doi.org/10.1016/s0003-9993(96)90042-8. PMID: 8629930.
68. Lundy CT, Doherty GM, Fairhurst CB. Botulinum toxin type a injections can be an effective treatment for pain in children with hip spasms and cerebral palsy. Dev Med Child Neurol. 2009;51(9):705–10. https://doi.org/10.1111/j.1469-8749.2009.03315.x. Epub 2009 Apr 21. PMID: 19459910
69. Rivard PF, Nugent AC, Symons FJ. Parent-proxy ratings of pain before and after botulinum toxin type a treatment for children with spasticity and cerebral palsy. Clin J Pain. 2009;25(5):413–7. https://doi.org/10.1097/AJP.0b013e31819a6d07. PMID: 19454875
70. Chaléat-Valayer E, Parratte B, Colin C, Denis A, Oudin S, Bérard C, Bernard JC, Bourg V, Deleplanque B, Dulieu I, Evrard P, Filipetti P, Flurin V, Gallien, et al. A French observational study of botulinum toxin use in the management of children with cerebral palsy: BOTULOSCOPE. Eur J Paediatr Neurol. 2011;15:439–48.
71. Pascale-Leone SI. Use of botulinum toxin in the preventive and palliative treatment of the hips in children with infantile cerebral palsy. Rev Neurol. 2003;37:80–2.
72. Barwood S, Baillieu C, Boyd R, Brereton K, Low J, Nattrass G, Graham HK. Analgesic effects of botulinum toxin a: a randomized, placebo-controlled clinical trial. Dev Med Child Neurol. 2000;42(2):116–21. https://doi.org/10.1017/s0012162200000220. PMID: 10698329
73. Copeland L, Edwards P, Thorley M, Donaghey S, Gascoigne-Pees L,Kentish M, Cert G, Lindsley J, McLennan K, Sakzewski L, Boyd RN. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. J Pediatr. 2014 Mar 12.[Epub ahead of print].

74. Jacobson D, Löwing K, Kullander K, Rydh BM, Tedroff K. A first clinical trial on botulinum toxin-A for chronic muscle-related pain in cerebral palsy. Front Neurol. 2021 Aug 16;12: 696218. https://doi.org/10.3389/fneur.2021.696218. PMID: 34484101; PMCID: PMC8415259.
75. Heinen F, Desloovere K, Schroeder AS, Berweck S, Borggraefe I, van Campenhout A, Andersen GL, Aydin R, Becher JG, Bernert G. The updated European consensus 2009 on the use of botulinum toxin for children with cerebral palsy. Eur J Paediatr Neurol. 2010;14:45–66.
76. Sätilä H. Over 25 years of pediatric botulinum toxin treatments: what have we learned from injection techniques, doses, dilutions, and recovery of repeated injections? Toxins (Basel). 2020 Jul 6;12(7):440. https://doi.org/10.3390/toxins12070440. PMID: 32640636; PMCID: PMC7404978.
77. Guyot P, Kalyvas C, Mamane C, Danchenko N. Botulinum toxins type A (bont-A) in the management of lower limb spasticity in children: a systematic literature review and bayesian network meta-analysis. J Child Neurol. 2019 Jun;34(7):371–381. https://doi.org/10.1177/0883073819830579. Epub 2019 Feb 25. PMID: 30803305; PMCID: PMC6512063.
78. Blumetti FC, Belloti JC, Tamaoki MJ, Pinto JA. Botulinum toxin type A in the treatment of lower limb spasticity in children with cerebral palsy. Cochrane Database Syst Rev. 2019 Oct 8;10(10):CD001408. https://doi.org/10.1002/14651858.CD001408.pub2. Epub ahead of print. PMID: 31591703; PMCID: PMC6779591.
79. Kim H, Kolaski K. Is botulinum toxin type a more effective and safer than other treatments for the management of lower limb spasticity in children with cerebral palsy? a Cochrane review summary with commentary. NeuroRehabilitation. 2021;49(1):161–4. https://doi.org/10.3233/NRE-218003. PMID: 34366300
80. Guyot P, Kalyvas C, Mamane C, Danchenko N. Botulinum toxins type A (bont-A) in the management of lower limb spasticity in children: a systematic literature review and bayesian network meta-analysis. J Child Neurol. 2019 Jun;34(7):371–381. https://doi.org/10.1177/0883073819830579. Epub 2019 Feb 25. PMID: 30803305; PMCID: PMC6512063.
81. Almina S, Karile Y, Audrone P, Indre B. Analgesic effect of botulinum toxin in children with cerebral palsy: a systematic review. Toxicon 2021 Aug;199:60–67. https://doi.org/10.1016/j.toxicon.2021.05.012. Epub 2021 Jun 1. PMID: 34081932.
82. Cosgrove AP, Graham HK. Botulinum toxin a prevents the development of contractures in the hereditary spastic mouse. Dev Med Child Neurol 1994 May;36(5):379–385. https://doi.org/10.1111/j.1469-8749.1994.tb11863.x. PMID: 8168656.
83. Lindsay C, Ispoglou S, Helliwell B, Hicklin D, Sturman S, Pandyan A. Can the early use of botulinum toxin in post stroke spasticity reduce contracture development? A randomised controlled trial. Clin Rehabil. 2021 Mar;35(3):399–409. https://doi.org/10.1177/0269215520963855. Epub 2020 Oct 11. PMID: 33040610; PMCID: PMC7944432.

Chapter 12
Treatment of Dystonic Pain with Botulinum Neurotoxins

Introduction

Dystonia is a movement disorder characterized by sustained twisting, turning, and abnormal postures. The recent classification defines two diagnostic axes, clinical and etiological [1]. Classification in the clinical axis is based on the age at onset, temporal pattern of dystonia, body distribution (focal, hemidystonia, segmental, multifocal, and generalized), and coexistence of other movement disorders, other neurological, or systemic manifestations. The etiological axis encompasses idiopathic, inherited, and acquired dystonia. Focal dystonias can be idiopathic, inherited, or acquired, and in any of these settings, can be painful.

In this chapter, four common and often painful focal dystonias will be discussed: cervical dystonia, oromandibular dystonia, focal dystonia in neurodegenerative disorders (Parkinson's disease and atypical Parkinson disorders), and post-traumatic/postsurgical limb dystonia.

Cervical Dystonia

Cervical dystonia (CD) is the most common form of idiopathic focal dystonia with an incidence of 1.07 to 1.2 per 100,000 person/years [2, 3] comparable with that of amyotrophic lateral sclerosis and Guillain–Barre syndrome (1.8 and 1.7/10,000, respectively) [3]; Nutt et al. [4] have reported a prevalence rate of 8.9/100,000 for CD in Minnesota. It is a late-onset dystonia which typically affects head and shoulder muscles. Dystonic head jerks (usually in the direction of limited head movements) and limitations of neck movement are the hallmarks of the disorder. Patients commonly complain about neck and shoulder pain which, for many, is the most disturbing symptom. Based on the pattern and posture of the head deviation,

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_12

cervical dystonia is classified as torticollis (head rotation), laterocollis (head tilt), retrocollis (head bent back), and anterocollis (head bent forward). Patients may have more than one type of cervical dystonias. The most common combination is torticollis and laterocollis.

In 1991, two retrospective studies from Baylor Medical College in Houston [5] and Columbia University in New York [6] defined characteristics of CD in a sizeable number of patients (in 300 and 266 patients, respectively). The basic data regarding CD was fairly similar between the two institutions regarding mean age at onset (41.9 vs. 41 years), female preponderance (1.9:1 vs. 1.5:1), and occurrence of pain (67% vs. 75%). In the Baylor series, pain was the presenting symptom in 17% of the patients.

Progress in genetic testing has identified several genes in the familial forms of cervical dystonia starting with DYT6, a form of cervico-cranial dystonia that begins at a young age and has a tendency to generalization. More recently, whole exome sequencing has identified several genetic abnormalities in families with adult-onset cervical dystonia [7]. GNAL gene which encodes for G protein (important in dopamine signaling) is another gene recently discovered in some patients with cervical dystonia [8]. A new GNAL gene mutation has been recently identified in a family with "Jerking type" of cervical dystonia [9].

Charles et al. [10] have published the results of a large multicenter, prospective study on assessment of clinical features and pain in CD (CD Probe study). The study was conducted at 88 centers in the United States and included 1037 participants. It compared the demographic and clinical profiles of CD patients with no/mild pain and those with moderate/severe pain. The study assessed the impact of pain and the motor component of CD on quality of life and compared the initial onabotulinumtoxin treatment paradigm between groups. The most common types of CD among the study's patients were torticollis (47.6%) and laterocollis (38.8%) with retrocollis and anterocollis considerably less common than the first two (5.3% and 5.7%, respectively).

The investigators assessed pain in this large cohort of patients with cervical dystonia through several questionnaires:

1. Pain numeric rating scale (PNRS) with a range of 0–10. Based on this questionnaire, level of pain was defined as mild (<4), moderate (4–6), and severe (7–10).
2. Cervical dystonia impact profile-58 (CDIP-58).
3. Pain subset (0–20) of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

A number of other parameters were also assessed through these scales including: severity of torticollis, motor disability, head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, psychosocial functioning, work productivity, and type of CD (anterocollis, laterocollis, retrocollis, or torticollis).

The results showed that 88.9% of the patients reported pain related to CD at baseline and 70.7% rated their CD-related pain as moderate or severe at baseline (PNRS score 4–10). Comparing the group with moderate to severe pain (4–10 on

the scale of 0–10) with the no or mild pain (0–3) group, patients with moderate to severe pain were significantly younger ($P < 0.0001$). Gender, race, and ethnicity were not different between the two groups. A higher percentage of patients among moderate to severe pain group was clinically disabled (14.7% vs. 4.9%) ($P < 0.0001$) and those in the moderate to severe pain group were twice more likely to have stopped work because of CD ($P < 0.019$). Moderate/severe pain was a significant predictor that employment status would be affected by CD ($P = 0.0001$). When the impact of pain on different subsets of CDIP-58 questionnaire was studied, pain had a larger impact than motor findings on mood, annoyance, sleep, head and neck, and upper limb activities, while pain and motor component had an equal impact on walking and psychosocial functioning.

Pain in CD is often described as a diffuse and sharp shooting pain. The pain sometimes takes a burning quality and, occasionally, radiates to the side of head deviation extending to the ipsilateral arm [11]. It has been shown that up to 30% of the patients with CD feel neck pain first before the development of dystonic posture and abnormal movements [12]. Approximately 10–20% of the patients with CD experience chronic headaches [13].

The Coll-Cap classification of CD classifies CD into Caput type (involved muscles are around the atlanto-occipital joint), and Collis type (involved muscles are around the cervical spine). Marciniec et al. [14] have found that pain in CD is 3.78 more common in patients who have the pure Caput type.

There may be a geographical factor influencing the report of pain intensity in association with the motor symptoms of CD. Patients in the United States, in general, report higher pain intensity assessed by the Toronto Spasmodic Torticollis Rating Scale (TWSTERS) than their European counterparts (mean score of 8.4 and 6, respectively) [15].

In search of mechanisms of pain in CD, some authors have reported conduction defects in C and A alpha pain fiber transmission indicating dysfunction of the ascending pain pathways (APP) [16]. However, more recent studies have provided evidence for normal APP in CD and abnormal conduction in the descending pain pathways (DPP) [17, 18] by testing the integrity of the DPP with the conditioned pain modulation response. The authors believe that this form of descending pathway dysfunction facilitates and maintains chronic pain.

Chan et al. [6] maintain the view that pain in CD is highly correlated with patients' postural and clinical features. In their carefully studied cohort, pain in CD correlated with severity of head turning ($P < 0.01$), constant head turning ($P < 0.05$), and presence of spasms ($P < 0.01$). Perhaps a high density of pain receptors in the neck muscles also plays a role in development of pain in cervical dystonia. The issue of pain in cervical dystonia and its treatment has been discussed in detail in several excellent reviews [19–21].

Treatment

Anticholinergic and gabaergic drugs (benzodiazepines and baclofen) are both effective in reducing the symptoms of cervical dystonia including pain. In the former category, trihexyphenidyl (6–30 mg/day) and benztropine (1–3 mg/ day) are the two most commonly used drugs. Baclofen (30–60 mg/day) and diazepam (10–30 mg/day) also improve symptoms of CD. Clonazepam (1–2.5 three times daily) is also helpful especially when CD is associated with cervical myoclonus. All aforementioned drugs need to be started at low dose and gradually built up over several weeks. Unfortunately, in some patients, satisfactory response requires using high doses of these drugs (>30 mg of trihexyphenidyl and > 60 mg of baclofen). Elderly patients have poor tolerance for anticholinergic medications and baclofen, especially in higher doses. Opioids are better avoided in treatment of pain in CD [19], as their use may lead to chronic substance abuse. Up to 11% of patients with a diagnosis of CD meet the criteria of substance abuse and opioids are among the leading causes [22]. Severity of neck pain, male gender, and mood disorders correlated with the use of opioids in CD.

In recent years, bilateral stimulation of globus pallidus has been employed for treatment of recalcitrant cases of cervical dystonia. Bilateral, chronic pallidal stimulation can improve the range of head movements and quality of life in patients with CD [23, 24]. In a recent report of five patients followed by chronic pallidal stimulation for 10–12 years, pallidal stimulation improved 53% of the total TWSTERS score and 54.1% of the severity score in CD but did not improve patient's neck pain significantly [25].

Effects of BoNTs on Pain Associated with Cervical Dystonia

Introduction of BoNTs for treatment of cervical dystonia (CD) has revolutionalized the management of this disorder. All types of BoNTs (ona, abo, inco, and rima, types A and B) have been proven effective and are now approved by the FDA for treatment of CD.

In most published studies, the rate of efficacy of BoNT injections in CD is over 80%, and the safety profile of BoNT in CD is unmatched by any other therapeutic agent used for treatment of this disorder. Treatment improves all major symptoms of CD and prevents development of contractures and radiculopathy [26]. BoNT therapy of CD may be more effective when it is combined with physiotherapy [27]. In a recent systematic review and meta-analysis [28], which assessed 18 studies and over 1900 patients, the mean duration of onaA effect was 93.2 and 95.2 days for fixed and random effect models, respectively. Doses of ≥180 units of onaA for treatment of cervical dystonia produced longer-lasting effects (107–109 days vs. 86–88 days for doses of <180 units).

One of the most important early observations in treatment of CD with botulinum neurotoxins (in this case, onaA) was the recognition that neck pain relief in CD often occurred before improvement of posture and limitation of head movement [29]. This important early observation suggested an analgesic effect for botulinum toxins in human subjects, independent from its other effects which were confirmed in the subsequent years.

Among the double-blinded studies (reviewed by this author), which have reported on the efficacy of BoNTs in cervical dystonia, 17 included assessment of pain. In the pioneering study of Tsui et al. [30], 14 of 16 patients with CD reported significant reduction of neck pain after administration of onabotulinumtoxinA into neck and shoulder muscles ($P = 0.002$). In a larger study of 55 patients, Greene et al. [31] also reported significant pain relief of their subjects six weeks after administration of onaA for CD. In another study of 23 patients, 19 of whom complained of pain, Lorentz et al. [32] reported pain relief in 12 of 19 patients who were injected by onaA, but only in 1 of 19 subjects was injected with saline ($P = 0.002$). Lew et al. [33] conducted an efficacy and safety study on 122 patients with CD evaluating the effects of 2500, 5000, and 10,000 units of rimaB against placebo (saline). Pain was assessed through the pain subset of TWSTRS and the visual analog scale (VAS). At four weeks, all three doses had produced significant pain relief compared to the placebo ($P < 0.05$). This relief was more pronounced for the largest dose used in the study ($P < 0.004$). Poewe et al. [34], in a study of 31 patients with neck pain and CD, also found a clear difference in pain improvement in favor of aboA (compared to placebo) at four weeks. The difference between the three dose groups of toxin (250, 500, and 1000 units), however, was not significant.

In 1999, two studies assessed the efficacy of rimabotulinumtoxin B (rimaB) in cervical dystonia and associated pain. In one study [35], the investigators compared the efficacy of 5000 and 10,000 units of rimaB with placebo in 109 patients using visual analog scale (VAS). At four weeks, significant reduction of pain was noted in both toxin groups compared to placebo- 5000 unit group ($P = 0.001$), 10,000 unit group ($P = 0.0002$). Overall, the TWSTRS scores improved more in the 10,000 unit group. In the same year, Brin et al. [36] published the results of another investigation on the efficacy of rimaB versus placebo in 77 patients with CD. Administration of 10,000 units of rimaB improved neck pain significantly at four weeks ($P < 0.001$). Wissel et al. [37] studied 68 patients with CD (with a minimum Tsui score of 9) comparing the effect of aboA (500 units) with placebo (saline). Patients were assessed at weeks 4, 8, and 12 with Tsui scale rating the severity of CD and pain. At week 4, 49 patients in the aboA group were pain-free versus 33 patients in the saline group ($P = 0.02$). In the following open phase of the study, the aboA group demonstrated significant pain relief ($P = 0.011$). Troung et al. [38] (2005) investigated the efficacy and safety of abobotulinumtoxinA (aboA, 500 units) in 80 patients with CD. Participants were followed up for 4 to 20 weeks, until they needed further treatment. The efficacy was assessed with TWSTRS at baseline and weeks 2, 4, 8, 12, 16, and 20 after treatment. Pain was evaluated via pain subset of TWSTRS or VAS scale of 0–100 mm. At four weeks, the reduction in VAS score was 13.4 for aboA

group and 1.9 for the placebo group ($P = 0.02$). This significant degree of pain reduction was also noted at week 8.

Between years 2010 and 2013, four multicenter studies in a sizeable number of patients with CD—associated pain and botulinumtoxin therapy—have been published [39–42]. Troung et al. [39] reported on the results of a multicenter study of 116 patients (55 aboA, 61 placebo) with CD after administration of 500 units of abobotulinumtoxinA (aboA) into neck and shoulder muscles. Four weeks after administration of aboA, the VAS score was reduced to 3.7 for the onaA group and 1.4 for the placebo group, respectively. Comella et al. [40] reported on the efficacy of two doses of incobotulinumtoxinA (incoA), 120 and 240 units, on 233 patients with cervical dystonia. Both doses were equally effective in improving all subsets of the TWSTRS scale including pain. The pain subset of TWSTRS (0–20) was markedly improved ($P < 0.0001$) at 4, 8, and 12 weeks. In another study [41], the efficacy of onabotulinumtoxinA (mean dose of 241 units) versus placebo was assessed in 170 patients with cervical dystonia (88 onaA, 82 placebo) using dystonia severity scale and physician global assessment scale at baseline and 6 weeks after injection. Evaluation of pain subset showed significant improvement ($P < 0.05$) at 2, 4, and 6 weeks post-treatment in the toxin group but not in the placebo group. In a multicenter double-blind, placebo-controlled study, Fernandez et al. [42] studied the effect of two doses (120 and 240 units) of incobotulinumtoxinA in 233 patients with CD. Pain was assessed through TWSTR's pain subset. At four weeks post injection, patients in both the 120 and 240 units groups demonstrated significant reduction of neck pain ($P < 0.0001$). There was no significant difference in pain response between the two prescribed doses of the neurotoxin. In contrast, Kaji et al. [43], using the TWSTRS pain subset, found doses of 2500 and 5000 units of rimabotulinumtoxinA (rimaA) ineffective in alleviating the pain of cervical dystonia at four weeks following toxin administration. A 10,000 unit dose, however, improved the pain significantly ($P < 0.05$). Mordin et al. [44] in a blinded and placebo-controlled study of 94 patients (47 toxin, 47 placebo) with cervical dystonia found that after treatment with onabotulinumtoxinA 66% and 72% of the patients reported pain relief (mild pain or no pain) at 4 and 12 weeks post treatment, respectively. The employed dose for treatment of CD was 500 units.

Poewe et al. [45] included pain assessment in a double-blind, placebo-controlled study of a large cohort of 369 patients, gathered from 61 centers. The efficacy of conventional abobotulinumtoxinA and ready-to-use abobotulinumtoxinA (prepared in liquid form) was compared with placebo. At 4 weeks, both abobulinumtoxinA and ready-to-use abotulinumtoxinA reduced patients' neck pain significantly compared to treatment with placebo ($P < 0.0001$).

The efficacy of BoNT treatment in alleviating the pain associated with cervical dystonia has been demonstrated in several prospective studies investigating large cohorts prospectively. The largest of such studies is the CD probe study. In this real-world, multicenter, prospective observational study, 1046 patients with no previous history of BoNT therapy were injected with onabotulinumtoxinA over 16 weeks with three cycles of injections. Beside significant improvements in TWSTRS scale and patient and physicians satisfaction with treatment, degrees of pain improvement

reported, after BoNT therapy, were also impressive. Significant pain relief was reported four to six weeks after each of the three cycles of treatment (6.1%, 72.4%, and 76.4%, respectively). The mean time of onset of pain relief was 7.1, 7.4, and 7.6 days post injection, respectively. All pain scales used showed significant improvement from baseline to the final visit ($P < 0.0001$) [46].

Comparator Studies

Same Toxin, Different Doses

Laubis-Herrmann et al. [47] studied the effect of high dose (500 units) and low dose (130 units) aboA injections upon pain relief in CD. Pain change was assessed by pain subset of TWSTRS at six weeks post injection. Subjects who received high dose reported pain relief ($P < 0.03$), while those on low dose only showed a trend toward improvement ($P < 0.06$). However, in most other measures of TWSTRS, the response did not differ between the two groups.

Different Toxins

Ranoux et al. [48] compared the efficacy of onaA and two different doses of aboA (3:1 ratio to onaA and 4:1 ratio to onaA) in a blinded study of 54 patients with CD. Patients' posture and motor function were assessed through Tsui scale (0–25), whereas pain was evaluated through the pain subset of TWSTRS. All three toxin preparations relieved pain. However, both aboA preparations were more effective than onaA in respect to pain relief ($P < 0.04$ and $P < 0.02$ for 3:1 and 4:1 rations, respectively). There was also a difference between the toxins in respect to side effects. OnaA produced considerably less dysphagia than either of the two preparations of aboA (3% vs. 15% and 17%, respectively).

Another comparator study [49] compared the efficacy of onaA with rimaB using TWSTRS in 139 CD patients (previously treated with onaA). Efficacy against symptoms of CD was evaluated at four weeks (pain was assessed via the pain subset of TWSTRS). Administration of both toxins relieved the neck pain significantly ($P < 0.001$). The drop in the pain score was 3.2 for onaA and 4 for rimaB, respectively (not a significant difference).

Pappert et al. [50], in a non-inferiority study, compared efficacy, safety, and duration of onaA (150 units) and rimaB (10,000 units) in 111 toxin-naïve patients with cervical dystonia (CD) subjects. Fifty-six of 111 subjects received placebo. Pain was assessed through the pain subset of TWSTRS along with other assessments at baseline and at four weeks following treatment. Both toxins were found to be

equally effective in improving symptoms of CD ($P = 0.001$) and pain. One patient in the rimaB group developed moderate dysphagia which improved spontaneously.

Another study [51] comparing 300 units of onabotulinumtoxinA with 300 units of Prosigne (Chinese toxin from Lanzhou Institute) found both equally effective in relieving pain at 4 and 16 weeks (using form SF36, pain subset). The study had 12 patients in each group (toxin and placebo). The authors suggested equal units for onaA and prosigne. Babarosa et al. [52] had also compared the efficacy of abobotulinumtoxinA (aboA) with Prosigne in a blinded study of 34 patients [52] (14 in aboA and 20 in Prosigne group). A dose ratio of 3 (aboA) to 1 (Prosigne) was used. Patients' responses were evaluated with TWSTRS scale which includes a pain subscale. Both toxins significantly improved both the movement and pain subscales of TWSTRS. There was no significant difference between the two as to the magnitude of pain relief.

Barn et al. [53] compared the efficacy of abobotulinumtoxinA with trihexyphenidyl (THP] in 66 patients with cervical dystonia. In the aboA group, subjects received two injections of the neurotoxin at week 0 and week 8 (mean dose 292 units and 262 units for weeks 0 and 8, respectively). The dose in the trihexyphenidyl group was up to 24 mg/day. Pain assessment (pain subset of TWSTRS) was performed at week 12 (4 weeks after the second injection). Although more patients in the aboA group demonstrated pain relief compared to the trihexyphenidyl group, the difference was not statistically significant.

Comment

Double-blind, placebo-controlled studies of BoNTs in CD indicate the efficacy of all four FDA-approved BoNTs in relieving CD-associated pain. Several studies with rimaB [33, 35, 43] and one study with onaA [47] have suggested that employment of larger dose of these toxins improves their efficacy. More studies are needed to verify these important observations. The clinicians, however, need to weigh the risk of complications versus the achievement of better response when considering the use of larger doses of BoNTs. Moreover, some comparative studies have found one toxin superior to the other for pain relief in CD; for example, aboA was reported to be superior to onaA in the study of Ranoux et al. [48]. This needs to be confirmed in blinded, comparative studies that investigate the analgesic effect of BoNTs in larger cohorts of CD and CD-associated pain. The same applies to the report of higher incidence of side effects with aboA compared to onaA in treatment of CD (48). The comparative study of trihexyphenidyl (THP) with abobotulinumtoxinA in CD suggested that aboA is more efficient than THP in improving the main CD symptoms, but there was no difference between the two in the case of pain relief [53]. This result may be due to the employment of a relatively low dose of aboA (less than 500 units) in this study; treatment with a larger dose of aboA may render a better analgesic effect.

Case 12.1

A 75-year-old man with history of progressive cervical dystonia and severe neck pain for over 10 years was referred to Yale Botulinum Toxin Treatment Clinic after failing to respond to conventional dystonia medications and analgesic drugs. On examination, the patient demonstrated advanced cervical dystonia with forced rotation of head and neck to the right side and intermittent left to right head jerks. There was marked hypertrophy of the left sternocleidomastoid (SCM) (Fig. 12.1) and right splenius capitis muscles. He rated severity of neck pain as 8 to 9 out of 10 (VAS). The patient was injected with a total of 400 units of onaA into the following muscles: left sternocleidomastoid: 80 units, left Trapezius: 60 units, left Splenius Capitis: 80 units. After a week, the head position improved and head jerks stopped. He noted significant relief from neck pain (remaining pain was rated 2 out of 10). The author followed him in the Yale Botulinum Toxin Clinic for 7 years during which the patient continued receiving onaA injections every 3 to 4 months maintaining a high degree of satisfaction.

Botulinum Toxin Treatment of Painful Dystonia in Neurodegenerative Disorders

Neurodegenerative disorders such as Parkinson's disease (PD) and atypical Parkinson disorders (corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy) are often associated with focal dystonia. Dystonia can be intermittent and take the form of dystonic spasms (involuntary toe flexion or foot inversion in PD) or manifest as persistent and progressive —the pattern most often

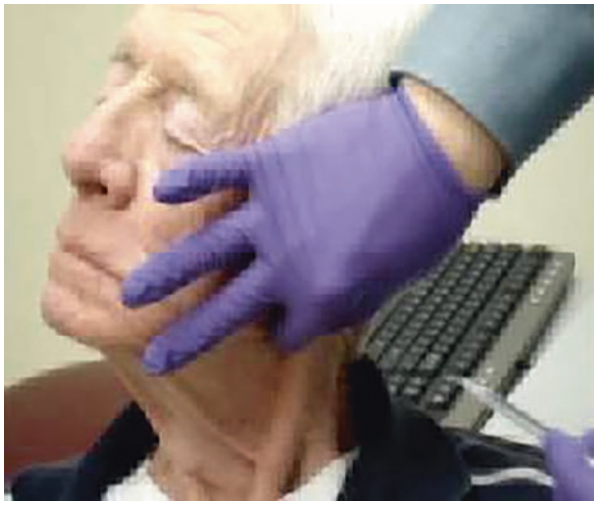

Fig. 12.1 (patient 12-1) Cervical dystonia with severe neck pain and marked hypertrophy of left SCM muscle

seen in corticobasal degeneration, but also sometimes in PD. Both forms can be painful and disabling. Focal dystonia in PD may be the result of PD itself or can be levodopa induced. Focal dystonia often develops during the course of PD but may precede classical PD symptoms by months or years [54]. The foot is most commonly involved.

In a study of 40 patients with pain in PD, Tinzzani et al. [55] identified 19 cases of dystonic pain. Of these 19, 17 patients manifested dystonic foot pain and two had painful cervical dystonia. Dystonic pain was significantly associated with a more advanced stage of PD and with motor complications of Parkinson's disease ($P = 0.001$).

Burmann et al. [56] described three types of pain in Parkinson's disease. Dystonic or dystonia-associated pain probably falls in the categories of nociceptive and/or central pain.

Several authors have reported successful treatment of painful hand and foot dystonia in PD with botulinum toxins in open label observations [57–61].

In a recent double-blind, placebo-controlled clinical trial, Rieu et al. [62] studied the effect of incobotulinumtoxinA on foot dystonia and associated pain with foot dystonia in PD. The toxin group consisted of 29 and the placebo group of 16 patients. In the toxin group, 15 patients received incoA (100 units) into the flexor digitorum brevis and 14 patients had the toxin injection (also 100 units) into flexor digitorum longus. The response of pain (using VAS) and foot dystonia to incoA and the response after placebo injection were evaluated at 6, 12, and 18 weeks. The authors noted a significant reduction of dystonia-associated pain in the group that received incoA into the flexor digitorum brevis at 6 and 18 post injection weeks.

In contrast to the above study, Bruno et al. [63] in a blinded study of 12 patients found no pain reduction. Five patients received botulinumtoxinA (not specified, probably onaA) and seven patients received placebo. The authors found no significant reduction of pain using VAS at 4 and 12 weeks after toxin therapy. However, dystonic pain showed greater reduction in the numerical pain rating scale (NRS) after four weeks compared to placebo (2.66 points compared to vs 0.75 points for placebo). In their earlier published open label study, 81% of the patients with PD reported pain relief [64].

Meuller et al. [65] reported on the treatment of 10 patients with focal upper limb dystonia in atypical Parkinson disorders. In two patients with corticobasal degeneration (CBD), administration of abobotulinumtoxinA into upper limb muscles (proximal and distal) improved dystonia and alleviated pain (method of pain assessment was not mentioned). In another study [60], administration of onaA into hand and forearm muscles improved dystonia and dystonic pain in three patients with CBD.

In my experience, EMG-guided botulinum toxin treatment is effective for treatment of pain associated with dystonic toe flexion or extension and foot inversion in patients with Parkinson's disease. The results are less gratifying in dystonic pain of atypical Parkinson disorders (APD) such as corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy, but I did have some patients with APD who found BoNT therapy worthwhile for their dystonic pain had opted to continue BoNT injections for years.

The following case reports demonstrate EMG-guided, BoNT treatment in two of my patients. One patient had painful toe flexion dystonia due to Parkinson's disease (case 12-2) and the other presented with painful foot inversion dystonia due to corticobasal degeneration (case 12-3).

Case 12-2

A 70-year--old female was referred to the Yale Movement Disorder Clinic for management of her symptoms of Parkinson's disease. She had carried the diagnosis of Parkinson's disease for two years. Her main complaints included diffuse stiffness of the upper and lower extremities, slowness of movements, postural instability, and intermittent painful toe flexion "spasms" which occurred several times daily. The timing of the painful foot dystonia showed no relationship to either timing or dosage of her medications. Her medications included carbidopa/levodopa 25/100, three times daily and primapexole, 0.5 mg, three times per day. Further increase of medications caused unacceptable dyskinesias.

On neurological examination, the main findings were confined to the motor system. She demonstrated bilateral moderate rigidity and hypokinesia (left more than right) and mild left-hand tremor. She had a slow and wide-based gait with slow turns. There were bilateral choreo-dystonic dyskinesias—more on the left side. During the 45-minute duration of her visit, she experienced a painful episode of involuntary flexion of all toes lasting several minutes. She measured the pain associated with this event at the level of 7–8 out of 10 in VAS scale.

Injection of onabotulinumtoxinA, 100 units into the flexor digitorum brevis (two sites) and 30 units into flexor hallucis (one site) (Fig. 12.2), under EMG guidance, resulted in marked reduction (less than one episode per month) of the dystonic foot

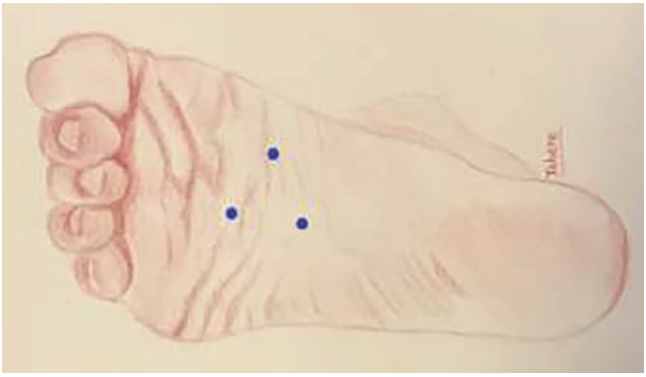

Fig. 12.2 (Patient-2) Painful toe flexion dystonia. One injection (30 units of onaA) into flexor hallucis longus and two injections into flexor digitorum brevis (40 units each of onaA). (Drawing courtesy of Tahere Safarpour, MD)

pain. The patient rated her response in the patient global impression of change (PGIC) as "much improved" and continued with BoNT treatment every three months. I followed her up for three years during which she reported satisfaction with a quarterly injection of onabotulinumtoxinA and experienced no side effects. Deep brain stimulation of the right subthalamic nucleus, 18 months after initiation of BoNT treatment, stopped the left-sided levodopa-induced dyskinesias and improved her left-sided hypokinesia and rigidity, but did not influence the episodic toe flexion dystonias.

Case -12-3

A 72-year-old woman complained of involuntary movements of her left leg which had begun insidiously a year earlier. The movements had gradually increased in intensity and the involved limb also developed increasing "stiffness." A magnetic resonance imaging of the head showed microvascular changes compatible with age, but no other abnormality. A Dopamine Transporter imaging (DAT) showed decreased level of dopamine bilaterally in the putamen. She was treated by a local neurologist with carbidopa/levodopa 100 mg four times daily. Since treatment failed to improve her symptoms, the patient asked for a second opinion and visited the Yale Movement Disorder Clinic approximately one year after the onset of her symptoms.

The patient had enjoyed good health throughout her life. She had a fall a few weeks before the onset of left leg movements during which she had landed on her left thigh. There was no family history of any neurological disorders. Her general medical examination was normal. Neurological examination showed involuntary, continuous, semi-rhythmic, and rhythmic movements of the left lower leg which were more prominent during action and when the limb was held against gravity. She also had nonvelocity-dependent, diffusely increased muscle tone in her left lower limb. There was no weakness and no pathological reflexes. A retrial of levodopa 250 mg, four times daily failed to improve the symptoms. Cervical, thoracic, and lumbar MRIs were normal. A paraneoplastic panel showed no abnormality, and cerebrospinal fluid examination was normal.

Over the next two years, the patient's symptoms gradually worsened. Muscle rigidity affected the upper extremity as well, and she developed a mild resting tremor in the left upper limb. The left lower limb became very rigid with progressive painful inversion dystonia of the left foot. She often did not know the position of her left limbs (upper or lower). The movements at times were irregular and, at times, semi-rhythmic, and the left foot assumed a dystonic inversion. She could no longer walk without assistance. Aggressive physical therapy offered modest help. EMG-guided injection of onabotulinumtoxinA improved dystonia and rigidity of the left side and relieved the foot pain. The following muscles were injected in the left leg: tibialis posterior (100 units), soleus (80 units, two sites), gastrocnemius (80 units, two sites), and hamstring (120 units, two sites). The patient's rating of global

impression of change (PGIC) in response to onaA treatment for pain was "much improved" and she continued with treatment every 3–4 months (2 years follow-up). She now carries the diagnosis of probable corticobasal degeneration based on the unilateral progressive nature of the disease, significant limb dystonia, limb apraxia, alien limb syndrome, and myoclonus.

Comment

Recent data suggest that, regardless of the underlying mechanism, pain in parkinsonism can be alleviated by botulinum toxin injections [66]. Proof of efficacy of BoNT therapy in dystonia-associated pain in Parkinson's disease and atypical Parkinson disorders awaits data from randomized blinded studies in large cohorts.

Post-traumatic Dystonia

Post-traumatic, focal limb dystonia is often painful. Most cases result from a physical injury to the limb (often hand or foot) or from postsurgical trauma (e.g., carpal tunnel syndrome). The prevalence of post-traumatic foot or hand dystonia is unknown. A retrospective review of 36 patients with foot dystonia, evaluated at Mayo Clinic between years 1996 and 2006, included 10 patients in whom the foot dystonia was post-traumatic. In some of these patients, the treatment with botulinum toxin improved dystonia and reduced pain [67].

Pedemonte et al. [68] reported their experience with onabotulinumtoxinA in 30 patients with post-traumatic oromandibular dystonia. The patients' main complaint was pain in the mandibular region. Many also suffered from bruxism. Five sites (3 into the masseter and 2 into the temporal muscles) were injected with onaA. Each injection site received 10 units for a total of 50 units per side. Pain was evaluated and scored from 0 to 3. The mean baseline pain score of the patients was 3. One month after toxin injection, the pain level dropped to 1; at two months post injection, patients reported no pain (0); pain returned after three months. Improvement of pain and oral mandibular dystonia was sustained with repeated injections over 36 months.

I have seen several patients with post-traumatic dystonia (mostly affecting the upper limb) with severe pain in the affected muscles. Injections with onabotulinumtoxinA under EMG guidance were helpful and in most patients relieved pain and satisfied the patient. Patient satisfaction was rated with the patient global impression of change (PGIC); the satisfaction rates of "improved" or "much improved" were considered significant. The patient described below was seen by me at Yale University's Botulinum Toxin Treatment Clinic and followed for several years with repeated injections.

Case 12-4

A 36-years-old female suffered from a right forearm injury after falling from a ladder. During the acute phase, the arm and hand were edematous and had multiple bruises. She was left with mild diffuse weakness of that hand and intermittent paresthesias in median and ulnar distribution. A few months after the trauma, she began to experience episodes of involuntary rapid finger flexion in the right hand associated with right wrist flexion, as well as concurrent sharp pains in the right wrist and forearm. The episodes occurred two to three times per day, lasted for several minutes (up to 15 minutes) and, afterwards, left a deep diffuse pain in the forearm which lasted for hours. She described the intensity of her pain as excruciating.

Injection of onabotulinumtoxinA under EMG guidance into the forearm muscles resulted in marked reduction in frequency and intensity of pain; the pain episodes were reduced from 2 to 3 per day to 1 per month and pain intensity from 10 in VAS scale dropped to 3 during the episode. The following muscles were injected with onaA every 3 months over 4 years of follow- up: flexor carpi ulnaris (60 units), flexor carpi radialis (40 units), flexor digitorum superficialis (total of 20 units injected into two points), flexor digitorum profondus (total 20 units injected into two points), lumbrical muscles (20 units, four points, Fig. 12.3). Repeated injections every three months continued to be helpful. After a year of treatment, the total dose of the toxin could be reduced to half with the same positive results.

Although many expert injectors of BoNTs do not include injection of lumbrical muscles when treating a clinched fist, this author, over the years, has found that injection of lumbricals is extremely helpful in relaxing the hand muscles and reducing the finger flexion. I injected through the palmer side of the hand at midplane of the hand into the belly of lumbricals (as shown by blue dots in Fig. 12.3). The dose for onaA, depending on the severity of dystonia or spasticity, varies between 2.5 and 5 units per each lumbrical. The palm of the hand is first numbed by Emla cream. Lumbrical injections are carried out using a 27.5 or 30 guage needle.

Comment

Open label studies and clinical observations suggest the efficacy of EMG-guided injections of onabotulinumtoxinA (Botox) in relieving pain of patients affected by post-traumatic foot and hand, as well as oromandibular dystonia. There is a need for high-quality (randomized, blinded, placebo-controlled) studies to verify these positive observations.

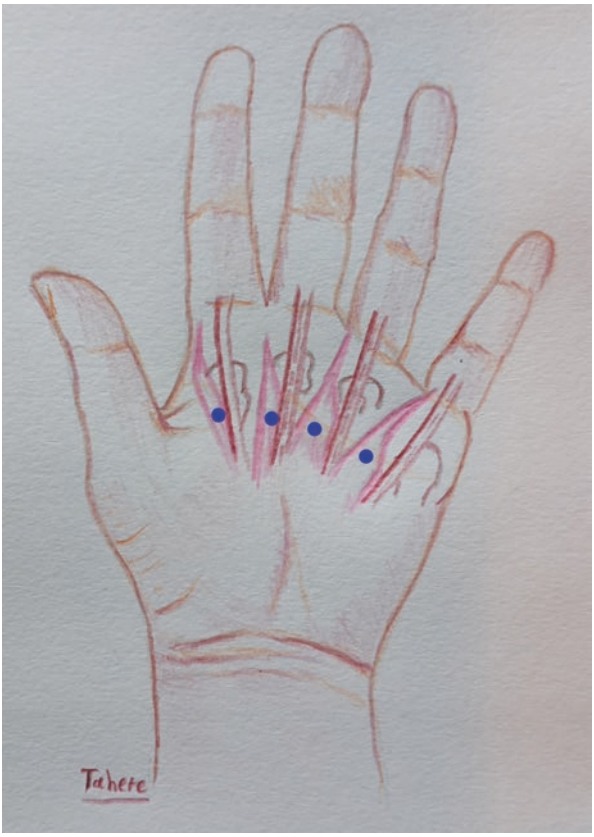

Fig. 12.3 (case 4) Site of injection into lumbrical muscles. Lumbrical muscles bend the fingers at metacarpophlyngeal joints. Each muscle is located medial to the tendon of finger flexors and can be injected at mid palm. (Drawing from Tahere Mousavi, MD)

References

1. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28:863–73.
2. Steeves TD, Day L, Dykeman J, Jette N, Pringsheim T. The prevalence of primary dystonia: a systematic review and meta-analysis. Mov Disord. 2012;27:1789–96.
3. Defazio G, Abbruzzese G, Livrea P, Berardelli A. Epidemiology of primary dystonia. Lancet Neurol. 2004 3(11):673–678. https://doi.org/10.1016/S1474-4422(04)00907-X. PMID: 15488460.
4. Nutt JG, Muenter MD, Aronson A, Kurland LT, Melton LJ. Epidemiology of focal and generalized dystonia in Rochester, 1968567-603. Minnesota Mov Disord. 1988;3:188–94.
5. Jankovic J, Leder S, Warner D, Schwartz K. Cervical dystonia: clinical findings and associated movement disorders. Neurology. 1991;41:1088–91.
6. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. Mov Disord. 1991;6:119–26.
7. Skogseid IM. Dystonia-new advances in classification, genetics, pathophysiology and treatment. Acta Neurol Scand Suppl. 2014;198:13–9.

8. Fuchs T, Saunders-Pullman R, Masuho I, Luciano MS, Raymond D, Factor S, Lang AE, Liang TW, Trosch RM, White S, Ainehsazan E, Hervé D, Sharma N, Ehrlich ME, Martemyanov KA, Bressman SB, Ozelius LJ. Mutations in GNAL cause primary torsion dystonia. Nat Genet. 2013;45:88–92.
9. Carecchio M, Panteghini C, Reale C, Barzaghi C, Monti V, Romito L, Sasanelli F, Garavaglia B. Novel GNAL mutation with intra-familial clinical heterogeneity: Expanding the phenotype. Park Relat Disord. 2016;23:66–71. https://doi.org/10.1016/j.parkreldis.2015.12.012. Epub 2015 Dec 18. PMID: 26725140.
10. Charles PD, Adler CH, Stacy M, Comella C, Jankovic J, Manack Adams A, Schwartz M, Brin MF. Cervical dystonia and pain: characteristics and treatment patterns from CD PROBE (Cervical Dystonia Patient Registry for Observation of onabotulinumtoxinA Efficacy). J Neurol. 2014;22. [Epub ahead of print]
11. Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. Pain. 1997;69(3):279–86. https://doi.org/10.1016/S0304-3959(96)03296-4. PMID: 9085302
12. Heinen F, Scheidt CE, Nickel T, Rayki O, Wissel J, Poewe W, Benecke R, Arnold G, Oertel W, Dengler R, Deuschl G. Spasmodic torticollis - a multicentre study on behavioural aspects II: signs, symptoms and course. Behav Neurol. 1996;9(2):81–8. https://doi.org/10.3233/BEN-1996-9204. PMID: 24487491
13. Barbanti P, Fabbrini G, Pauletti C, Defazio G, Cruccu G, Berardelli A. Headache in cranial and cervical dystonia. Neurology 2005;64(7):1308–1309. https://doi.org/10.1212/01.WNL.0000156909.13677.FF. PMID: 15824376.
14. Marciniec M, Szczepańska-Szerej A, Popek-Marciniec S, Rejdak K. Pain incidence in cervical dystonia is determined by the disease phenotype. J Clin Neurosci. 2020;79:133–136. https://doi.org/10.1016/j.jocn.2020.07.069. Epub 2020 Aug 5. PMID: 33070882.
15. Trosch R, Misra VP, Om S, Maisonobe P. Poster 498 geographic differences in the characteristics of cervical dystonia patients. PM R. 2016;8(9S):S322. https://doi.org/10.1016/j.pmrj.2016.07.415. Epub 2016 Sep 24. PMID: 27673242.
16. Paracka L, Wegner F, Blahak C, Abdallat M, Saryyeva A, Dressler D, Karst M, Krauss JK. Sensory alterations in patients with isolated idiopathic dystonia: an exploratory quantitative sensory testing analysis. Front Neurol. 2017; 8:553. https://doi.org/10.3389/fneur.2017.00553. PMID: 29089923; PMCID: PMC5650962.
17. Tinazzi M, Valeriani M, Squintani G, Corrà F, Recchia S, Defazio G, Berardelli A. Nociceptive pathway function is normal in cervical dystonia: a study using laser-evoked potentials. J Neurol. 2012;259(10):2060–2066. https://doi.org/10.1007/s00415-012-6454-1. Epub 2012 Feb 18. PMID: 22349875.
18. Tinazzi M, Squintani GM, Bhatia KP, Segatti A, Donato F, Valeriani M, Erro R. Pain in cervical dystonia: evidence of abnormal inhibitory control. Parkinsonism Relat Disord. 2019; 65:252–255. https://doi.org/10.1016/j.parkreldis.2019.06.009. Epub 2019 Jun 15. PMID: 31227336.
19. Rosales RL, Cuffe L, Regnault B, Trosch RM. Pain in cervical dystonia: mechanisms, assessment and treatment. Expert Rev Neurother. 2021 29:1–10. https://doi.org/10.1080/14737175.2021.1984230. Epub ahead of print. PMID: 34569398.
20. Matteo C, Daniele B, Isabella B, Annalisa M, Fabrizia D, Viola B, Arianna T, Gina F, Massimo P, Antonella C, Giovanni F, Giovanni D, Alfredo B. Motor and non-motor subtypes of cervical dystonia. Parkinsonism Relat Disord. 2021;88:108–113. https://doi.org/10.1016/j.parkreldis.2021.06.008. Epub 2021 Jun 18. PMID: 34174552.
21. Monaghan R, Cogley C, Burke T, McCormack D, O'Riordan S, Ndukwe I, Hutchinson M, Pender N, O'Keeffe F. Non-motor features of cervical dystonia: cognition, social cognition, psychological distress and quality of life. Clin Park Relat Disord. 2020 4;100084. https://doi.org/10.1016/j.prdoa.2020.100084. PMID: 34316662; PMCID: PMC8299967.
22. Mahajan A, Jankovic J, Marsh L, Patel A, Jinnah HA, Comella C, Barbano R, Perlmutter J, Patel N; Members of the Dystonia Coalition. Cervical dystonia and substance abuse. J Neurol. 2018;265(4):970–975. https://doi.org/10.1007/s00415-018-8840-9. Epub 2018 Mar 22. PMID: 29569175.

23. Walsh RA, Sidiropoulos C, Lozano AM, Hodaie M, Poon YY, Fallis M, Moro E. Bilateral pallidal stimulation in cervical dystonia: blinded evidence of benefit beyond 5 years. Brain. 2013;136:761–9.
24. Dinkelbach L, Mueller J, Poewe W, Delazer M, Elben S, Wolters A, Karner E, Wittstock M, Benecke R, Schnitzler A, Volkmann J, Südmeyer M. Cognitive outcome of pallidal deep brain stimulation for primary cervical dystonia: One year follow up results of a prospective multicenter trial. Parkinsonism Relat Disord. 2015; 8:976–980. https://doi.org/10.1016/j.parkreldis.2015.06.002. Epub 2015 Jun 4. PMID: 26074391.
25. Kaelin-Lang A, You H, Burgunder JM, Lönnfors-Weitze T, Loher TJ, Taub E, Isaias IU, Krauss JK, Michael Schüpbach WM. Bilateral pallidal stimulation improves cervical dystonia for more than a decade. Parkinsonism Relat Disord. 2020;81:78–81. https://doi.org/10.1016/j.parkreldis.2020.10.028. Epub 2020 Oct 15. PMID: 33075700.
26. Jankovic J. Treatment of cervical dystonia with botulinum toxin. Mov Disord. 2004;19(Suppl 8):S109–15.
27. Tassorelli C, Mancini F, Balloni L, Pacchetti C, Sandrini G, Nappi G, Martignoni E. Botulinum toxin and neuromotor rehabilitation: an integrated approach to idiopathic cervical dystonia. Mov Disord. 2006;21:2240–3.
28. Marsh WA, Monroe DM, Brin MF, Gallagher CJ. Systematic review and meta-analysis of the duration of clinical effect of onabotulinumtoxinA in cervical dystonia. BMC Neurol. 2014;14:91.
29. Jankovic J, Schwartz K. Botulinum toxin injections for cervical dystonia. Neurology. 1990;40:277–80.
30. Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. Lancet. 1986;2:245–7.
31. Greene P, Kang U, Fahn S, Brin M, Moskowitz C, Flaster E. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. Neurology. 1990;40:1213–8.
32. Lorentz IT, Subramaniam SS, Yiannikas C. Treatment of idiopathic spasmodic torticollis with botulinum toxin A: a double-blind study on twenty-three patients. Mov Disord. 1991;6:145–50.
33. Lew MF, Adornato BT, Duane DD, Dykstra DD, Factor SA, Massey JM, Brin MF, Jankovic J, Rodnitzky RL, Singer C, Swenson MR, Tarsy D, Murray JJ, Koller M, Wallace JD. Botulinum toxin type B: a double-blind, placebo-controlled, safety and efficacy study in cervical dystonia. Neurology. 1997;49:701–7.
34. Poewe W, Deuschl G, Nebe A, Feifel E, Wissel J, Benecke R, Kessler KR, Ceballos-Baumann AO, Ohly A, Oertel W, Künig G. What is the optimal dose of botulinum toxin A in the treatment of cervical dystonia? Results of a double blind, placebo controlled, dose ranging study using Dysport. German Dystonia Study Group. J Neurol Neurosurg Psychiatry. 1998;64:13–7.
35. Brashear A, Lew MF, Dykstra DD, Comella CL, Factor SA, Rodnitzky RL, Trosch R, Singer C, Brin MF, Murray JJ, Wallace JD, Willmer-Hulme A, Koller M. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. Neurology. 1999;53:1439–46.
36. Brin MF, Lew MF, Adler CH, Comella CL, Factor SA, Jankovic J, O'Brien C, Murray JJ, Wallace JD, Willmer-Hulme A, Koller M. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. Neurology. 1999;53:1431–8.
37. Wissel J, Kanovsky P, Ruzicka E, Bares M, Hortova H, Streitova H, Jech R, Roth J, Brenneis C, Müller J, Schnider P, Auff E, Richardson A, Poewe W. Efficacy and safety of a standardized 500 unit dose of Dysport (clostridium botulinum toxin type A haemaglutinin complex) in a heterogeneous cervical dystonia population: results of a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel group study. J Neurol. 2001;248:1073–8.
38. Truong D, Duane DD, Jankovic J, Singer C, Seeberger LC, Comella CL, Lew MF, Rodnitzky RL, Danisi FO, Sutton JP, Charles PD, Hauser RA, Sheean GL. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. Mov Disord. 2005;20:783–91.

39. Truong D, Brodsky M, Lew M, Brashear A, Jankovic J, Molho E, Orlova O, Timerbaeva S. Global Dysport Cervical Dystonia Study Group. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. Parkinsonism Relat Disord. 2010;16:316–23.
40. Comella CL, Jankovic J, Truong DD, Hanschmann A, Grafe S, U.S. XEOMIN Cervical Dystonia Study Group. Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN®, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia. J Neurol Sci. 2011;308:103–9.
41. Charles D, Brashear A, Hauser RA, Li HI, Boo LM, Brin MF. CD 140 Study Group. Efficacy, tolerability, and immunogenicity of onabotulinumtoxina in a randomized, double-blind, placebo-controlled trial for cervical dystonia. Clin Neuropharmacol. 2012;35:208–14.
42. Fernandez HH, Pappert EJ, Comella CL, Evidente VG, Truong DD, Verma A, Jankovic J. Efficacy and safety of incobotulinumtoxinA in subjects previously treated with botulinum toxin versus toxin-naïve subjects with cervical dystonia. Tremor Other Hyperkinet Mov (NY). 2013; 3. pii: tre-03-140-2921-1. Print 2013.
43. 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; 65:203–211.
44. Mordin M, Masaquel C, Abbott C, Copley-Merriman C. Factors affecting the health-related quality of life of patients with cervical dystonia and impact of treatment with abobotulinumtoxinA (Dysport): results from a randomised, double-blind, placebo-controlled study. BMJ Open. 2014 Oct 16;4(10):e005150. https://doi.org/10.1136/bmjopen-2014-005150. PMID: 25324317; PMCID: PMC4201999.
45. Poewe W, Burbaud P, Castelnovo G, Jost WH, Ceballos-Baumann AO, Banach M, Potulska-Chromik A, Ferreira JJ, Bihari K, Ehler E, Bares M, Dzyak LA, Belova AN, Pham E, Liu WJ, Picaut P. Efficacy and safety of abobotulinumtoxinA liquid formulation in cervical dystonia: A randomized-controlled trial. Mov Disord. 2016 Nov;31(11):1649–1657. https://doi.org/10.1002/mds.26760. Epub 2016 Sep 21. PMID: 27653448.
46. Charles PD, Manack Adams A, Davis T, Bradley K, Schwartz M, Brin MF, Patel AT. Neck pain and cervical dystonia: treatment outcomes from CD PROBE (cervical dystonia patient registry for observation of onabotulinumtoxinA efficacy). Pain Pract. 2016 Nov;16(8):1073–1082. https://doi.org/10.1111/papr.12408. Epub 2016 Feb 23. PMID: 26910788.
47. Laubis-Herrmann U, Fries K, Topka H. Low-dose botulinum toxin-a treatment of cervical dystonia – a double-blind, randomized pilot study. Eur Neurol. 2002;47(4):214–21. https://doi.org/10.1159/000057902. PMID: 12037435
48. Ranoux D, Gury C, Fondarai J, Mas JL, Zuber M. Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. J Neurol Neurosurg Psychiatry. 2002 Apr;72(4):459–462. https://doi.org/10.1136/jnnp.72.4.459. PMID: 11909903; PMCID: PMC1737843.
49. Comella CL, Jankovic J, Shannon KM, Tsui J, Swenson M, Leurgans S, Fan W. Dystonia Study Group. Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. Neurology. 2005;65:1423–9.
50. Pappert EJ, Germanson T, Myobloc/Neurobloc European Cervical Dystonia Study Group. Botulinum toxin type B vs. type A in toxin-naïve patients with cervical dystonia: Randomized, double-blind, noninferiority trial. Mov Disord. 2008;15(23):510–7.
51. 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.
52. Barbosa PM, Rodrigues GR, de Oliveira DS, de Souza CP, Tumas V. Comparison between Dysport and Prosigne in the treatment of cervical dystonia. Clin Neuropharmacol. 2015 Nov-Dec;38(6):221–6. https://doi.org/10.1097/WNF.0000000000000107. PMID: 26536017.
53. Brans JW, Linderboom R, Snoek JW, Zwarts MJ, van Weerden TW, Brunt ER, van Hilten JJ, van der Kamp W, Prins MH, Speelman JD. Botulinum toxin versus trihexyphenidyl in cervical dystonia: a prospective, randomized, double-blind trial. Neurology. 1996;46:1066–72.

54. LeWitt PA, Burns RS, Newman RP. Dystonia in untreated parkinsonism. Clin Neuropharmacol. 1986;9:293–7.
55. Tinazzi M, Del Vesco C, Fincati E, Ottaviani S, Smania N, Moretto G, Fiaschi A, Martino D, Defazio G. Pain and motor complications in Parkinson's disease. J Neurol Neurosurg Psychiatr. 2006;77:822–5.
56. Buhmann C, Kassubek J, Jost WH. Management of pain in Parkinson's disease. J Parkinsons Dis. 2020;10(s1):S37–S48. https://doi.org/10.3233/JPD-202069. PMID: 32568113; PMCID: PMC7592654.
57. Pacchetti C, Albani G, Martignoni E, Godi L, Alfonsi E, Nappi G. 'Off' painful dystonia in Parkinson's disease treated with botulinum toxin. Mov Disord. 1995;10:333–6.
58. Duarte J, Sempere AP, Coria F, Claveria LE, Frech FA, Mataix AL, Martinez E. Isolated idiopathic adult-onset foot dystonia and treatment with botulinum toxin. J Neurol. 1995;242:114–5.
59. Jankovic J, Tintner R. Dystonia and Parkinsonism. Parkinsonism Relat Disord. 2001;8:109–21.
60. Cordivari C, Misra VP, Catania S, Lees AJ. Treatment of dystonic clenched fist with botulinum toxin. Mov Disord. 2001;16:907–13.
61. Sheffield JK, Jankovic J. Botulinum toxin in the treatment of tremors, dystonias, sialorrhea and other symptoms associated with Parkinson's disease. Expert Rev Neurother. 2007;7:637–47.
62. Rieu I, Degos B, Castelnovo G, Vial C, Durand E, Pereira B, Simonetta-Moreau M, Sangla S, Fluchère F, Guehl D, Burbaud P, Geny C, Gayraud D, Ory-Magne F, Bouhour F, Llinares E, Derost P, Marques A, Durif F. Incobotulinum toxin A in Parkinson's disease with foot dystonia: a double blind randomized trial. Parkinsonism Relat Disord. 2018 Jan;46:9–15. https://doi.org/10.1016/j.parkreldis.2017.10.009. Epub 2017 Oct 19. PMID: 29102441.
63. Bruno V, Freitas ME, Mancini D, Lui JP, Miyasaki J, Fox SH. Botulinum toxin type A for pain in advanced Parkinson's disease. Can J Neurol Sci. 2018 Jan;45(1):23–29. https://doi.org/10.1017/cjn.2017.245. PMID: 29334040.
64. Bruno VA, Fox SH, Mancini D, Miyasaki JM. Botulinum toxin use in refractory pain and other symptoms in Parkinsonism. Can J Neurol Sci. 2016 Sep;43(5):697–702. https://doi.org/10.1017/cjn.2016.279. Epub 2016 Aug 12. PMID: 27514242.
65. Müller J, Wenning GK, Wissel J, Seppi K, Poewe W. Botulinum toxin treatment in atypical parkinsonian disorders associated with disabling focal dystonia. J Neurol. 2002;249:300–4.
66. Cardoso F. Botulinum toxin in parkinsonism: the when, how, and which for botulinum toxin injections. Toxicon. 2018 Jun 1;147:107–110. https://doi.org/10.1016/j.toxicon.2017.08.018. Epub 2017 Aug 23. PMID: 28837826.
67. McKeon A, Matsumoto JY, Bower JH, Ahlskog JE. The spectrum of disorders presenting as adult-onset focal lower extremity dystonia. Parkinsonism Relat Disord. 2008;14:613–9.
68. Pedemonte C, Pérez Gutiérrez H, González E, Vargas I, Lazo D. Use of onabotulinumtoxinA in post-traumatic oromandibular dystonia. J Oral Maxillofac Surg. 2015 Jan;73(1):152–157. https://doi.org/10.1016/j.joms.2014.07.027. Epub 2014 Jul 30. PMID: 25315313.

Chapter 13
Botulinum Toxin Treatment of Piriformis Syndrome

Introduction

In 1928, Yeomin published an article in *Lancet* mentioning piriformis muscle as a cause of sciatic and low back pain for the first time [1]. The term "piriformis syndrome" was coined by Robinson in 1947 [2]. Piriformis syndrome (PS) is defined as a clinical condition characterized by pain in the buttocks, often worsened by prolonged sitting. It is believed that PS is caused by entrapment of sciatic nerve or its roots near the ischial tuberosity by either a hypertrophied or an anomalous piriformis muscle. Due to the difficulty in finding an exact pathology in many patients, lack of clear neuroimaging abnormalities and electrophysiological data, some specialists have challenged the existence of this syndrome [3, 4]. It is currently believed, however, that the syndrome exists and is the cause of buttock pain and sciatica in a sizeable number of patients.

The true incidence of piriformis syndrome is not known. Investigators have estimated that 0.3–6% of all cases of sciatica and low back pain represent PS [5–7]. Based on these estimates, PS would affect over approximately, 2.4 million people in the United States annually posing a significant health issue and a challenge to clinicians. Females are more commonly affected. The onset of symptoms is usually at middle age.

The cause of piriformis syndrome, in many cases, remains unknown. Hypertrophied piriformis muscle or anomalous piriformis muscle pressing against sciatic nerves or sciatic roots, early division of sciatic nerve, as well as trauma to the pelvis and gluteal area are considered plausible etiologies. Less common causes include disease of the sacroiliac joint, intragluteal injections, myositis, hematoma, abscess, and regional neoplasm.

Pain is the major symptom of PS, and it is often present during prolonged sitting or squatting [8]. The pain is felt mainly in the buttock and may radiate down the thigh. Less commonly, it is felt in the lower back region. On examination, pressure

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_13

Table 13.1 Clinical maneuvers used for diagnosis of piriformis syndrome

Beaty maneuver: Patient lying in lateral decubitus position, actively abducts the extended thigh
Pace maneuver: Patient sits on a table and adducts the thigh against the examiner's hand
Feiberg maneuver: Patient in supine position with leg extended, the examiner passively rotates the whole leg internally
Fair maneuver: Patient in supine position, the examiner passively flexes, adducts, and rotates the thigh internally

over the area of sciatic notch may induce pain. In a review of 50 previously published papers on piriformis syndrome, Hopyian et al. [6] found buttock pain (50–95%), pain aggravated by sitting (39–97%), and external tenderness near the greater sciatic notch (59–92%) as the most common presenting symptoms of the piriformis syndrome. The piriformis sign is described as a tonic external rotation of the leg and was observed in 38.5% of the patients in one study [9]. A small number of patients may demonstrate mild muscle weakness related to sciatic nerve dysfunction. Diminished knee and ankle jerks occur infrequently. Certain maneuvers that generate buttock pain are considered supportive of the diagnosis of piriformis syndrome (Table 13.1). More details of clinical signs and symptoms of piriformis syndrome have been published in several recent reviews [6–8, 10–12].

In 2002, Fishman et al. [13] proposed the following criteria for diagnosis of PS:

1. Positive Lasegue sign is flexion of the thigh when the leg is extended at 45°.
2. Buttock pain during FAIR maneuver.
3. Tenderness to touch at the sciatic notch or prolonged peroneal H reflex when elicited during the FAIR maneuver.

Absence of neuropathy or myopathy in electrodiagnostic studies also supports the diagnosis of PS. Campbell and Landau [14] challenged some components of this criteria, noting that the Lasegue sign is nonspecific and the peroneal H reflex is not that reliable.

Anatomy

Piriformis, a triangular-shaped muscle, originates from the anterior border of the second, third, and fourth sacral bone segments and the superior margin of the greater sciatic notch. It attaches to the superior margin of the greater trochanter after passing inferolaterally through the greater sciatic foramen. The muscle is located deep in the thigh and is under the large bulk of gluteus maximus muscle. The superior and inferior gemulus muscles lie inferior to the piriformis muscle (Fig. 13.1). The ventral rami of S1 and S2 nerve roots join and form the piriformis nerve which innervates the piriformis muscle. Piriformis muscle externally rotates an extended leg and adducts a flexed leg [15]. The sciatic nerve is in close proximity to the piriformis muscle. Ventral rami of L4 to S3 nerve roots join and form the sciatic nerve at

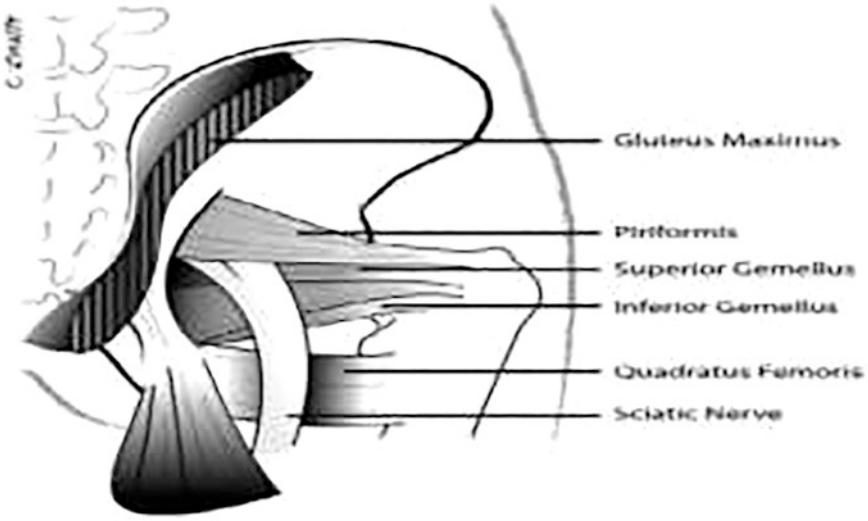

Fig. 13.1 Anatomy of piriformis muscle from Miller et al. [5]. (Reprinted with permission from John Wiley and sons)

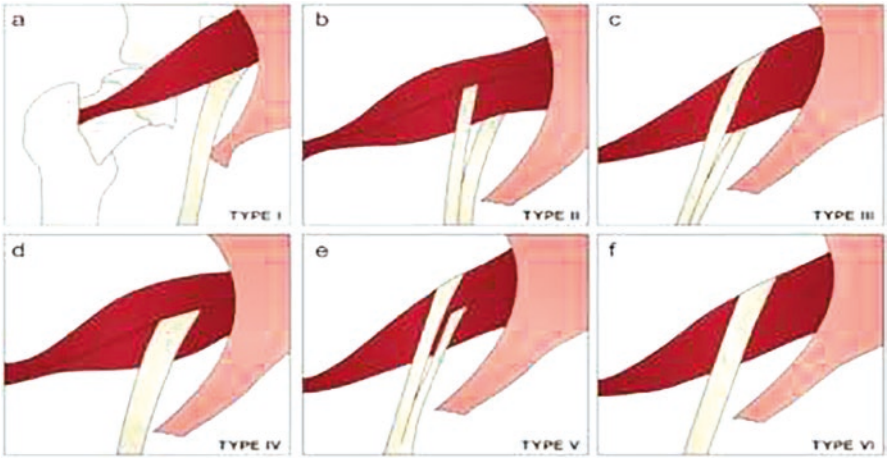

Fig. 13.2 Anatomical variations of sciatic nerve in relation to the piriformis muscle according to Natsis et al., in Surgical Radiological Anatomy 2014 [16]. (Drawing courtesy of Tahere Moussavi, M.D.)

the inferior edge of the piriformis muscle (Fig. 13.1). This proximity makes the nerve vulnerable to pressure from an enlarged or overactive muscle. Natsis et al. [16] examined the relation of piriformis muscle to the sciatic nerve in 147 cadavers. Six variations of the anatomical relation of sciatic nerve to the piriformis muscle have been described (Fig. 13.2). The most common variant noted in about 90% of

cases is that the entire nerve trunk passes under the inferior border of the piriformis muscle (Fig. 13.2, variant 1). Other variants are seen in approximately 10% of the cases.

Currently, the precise contribution of the uncommon variants to the development of piriformis syndrome has not been established. Some authors have suggested that when the nerve trunk or one of its branches (i.e., the peroneal) go through the muscle (variants 2 and 4, Fig. 13.2), the nerve becomes more susceptible to piriformis contraction. Future studies with focus on clinico-anatomical correlation and with more refined neuroimaging techniques could verify or refute these claims.

Pathophysiology of the Piriformis Syndrome

There are currently two schools of thought regarding the mechanism of pain development which is the main symptom of the piriformis syndrome. One group considers the piriformis syndrome as a form of entrapment disorder in which pressure from the tense and contracted piriformis muscle against the sciatic nerve or its branch, peroneal nerve (which in some individuals goes through the muscle), causes pain and discomfort in the buttock. Others postulate that PS is caused by an anomaly intrinsic to the piriformis muscle. The nature of this anomaly could be a large piriformis muscle or a tense and hyperactive one (dystonic) or both. The two proposed mechanisms (entrapment versus intrinsic muscle disorder) are not mutually exclusive and may co-exist. Recent modern neuroimaging techniques have helped to discern different pathologies in patients affected by PS. In one study [17], authors found abnormalities in CT or MRI in 63.8% of 116 patients affected by PS. Enlargement of piriformis muscle was found in 45.9% of the patients with 40.5% showing abnormal signal intensity/density in the muscle. In 25.7% of the patients, there were abnormalities of the sciatic nerve consistent with sciatic neuritis. Among other pathologies, a space-occupying lesion was presented as the most common pathology.

Treatment of the Piriformis Syndrome (PS)

The current medical and surgical treatments of piriformis syndrome have been described recently in an updated comprehensive review [18].

Nonpharmacological approaches include physical therapy, acupuncture, and dry needling. Physical therapy is focused on stretching exercises of the piriformis muscles. One part of the stretching program includes FAIR maneuver (Table 13.1) which, at the beginning, may be uncomfortable due to the associated induced pain. Gulledge et al. [19] measured the length of piriformis muscle by CT scan at three positions, supine and two supine positions with added stretch in adduction and external rotation. The stretches increased the length of the piriformis muscle by

12%. Heat and ultrasound therapy may enhance the effects of the stretching exercises [10]. Acupuncture has helped some patients with PS; triple acupuncture produced better results than the conventional one [20]. In one randomized study, dry needling of piriformis muscle under ultrasound (16 patients) improved patients' pain (measured by VAS) after one week compared to 16 controls ($P = 0.007$) [21]. Nonsteroidal anti-inflammatory drugs, muscle relaxants, and analgesics commonly used for neuropathic pain such as gabapentin and pregabalin may offer help in some patients.

When nonpharmacological approaches and pharmacological treatments fail in PS and chronic pain interferes with daily tasks, injection of anesthetic agents or corticosteroids into the piriformis muscle may relieve pain. Unfortunately, high-quality studies are not available to define the efficacy of such injections in patients with piriformis syndrome. In a large retrospective study, however, Fishman et al. reported their 10-year experience in over 500 patients with PS who had received these injections [13]. In most patients, injections were done via anatomical landmarks and without EMG guidance. Each patient received 1.5 ml of 2% lidocaine mixed with 0.5 ml (20 mg) of triamcinolone. The injecting needle was 3.5 in long (gauge 23–25). Patients were followed every few months up to 48 months; significant improvement of pain was noted in 71% of the patients. The duration of pain relief after steroid injections is unclear and deserves further investigation. Currently, surgical treatment of piriformis syndrome is rarely performed and is limited to those cases in which magnetic resonance imaging defines a distinct pathology (tumor, abscess, vascular anomaly).

Botulinum Toxin Treatment of Piriformis Syndrome

The first case series suggesting the efficacy of botulinum toxin in relieving pain of piriformis syndrome was published by Fanucci et al. in 2001 [22]. In an open label observation, 30 patients received 200 units of onabotulinumtoxinA (onaA Botox) into the piriformis muscle under computed tomography (CT) guidance. A response was considered significant if pre-injection pain induced by forceful flexion/internal rotation of the involved leg resolved after injection. Twenty-six of 30 patients experienced pain relief when assessed 5–7 days after treatment with onaA. The four patients who did not get any relief from pain received a second injection which then, according to the authors, relieved the pain.

Double-Blind, Placebo-Controlled Studies of BoNTs in Piriformis Syndrome

Three double-blind, placebo-controlled studies have evaluated the efficacy of botulinumtoxinA in pain relief among patients with piriformis syndrome [23–25].

Fishman et al. [23], using the criteria cited above for diagnosis of PS, blindly studied three groups of subjects with intramuscular injections under electromyographic guidance. Group 1 consisted of 26 patients who received 200 units of onabotulinumtoxinA (onaA). In group II, 37 subjects received triamcinolone 20 mg mixed with 2% lidocaine 2% (T/L). In group III, 24 subjects received normal saline. Patients were examined every 2 weeks after injection for a total of 12 weeks. A significant response was considered as a 50% reduction in pain intensity (using VAS), compared to baseline at one or both of the last two evaluations. A significant response was noted in 65% of onaA group, 32% of T/L group, and 6% of the placebo group ($P = 0.001$ and $P = 0.005$, respectively). No side effects were noted.

Childers et al. [24] conducted a prospective, placebo-controlled, double-blind, cross-over study with onaA and saline in nine patients with piriformis syndrome. After an initial injection of 100 units of onaA into the piriformis muscle under fluoroscopic guidance, pain was assessed over an eight-week period with visual analog scale (VAS). This was followed by a second injection after a four-week washout period. Patients served as their own controls. The authors noted significant decrease in pain, measured by VAS, from day 4 to day 32 postonabotulinum-A injection ($P < 0.05$); there was also significant improvement of daily routine activities from day 5 to day 59 after onaA injection. No subject reported any side effect.

More recently, Fishman et al., in a double-blind placebo-controlled study, assessed the efficacy of incobotulinumtoxinA (Xeomin, incoA) in 56 patients with PS [25]. The patients in the toxin group received 300 units of incoA diluted in 3 ml of normal saline, whereas the patients in the placebo group received the same volume of saline. The total toxin dose was divided by four; 75 units were injected into the piriformis muscle at four sites. Inclusion criteria, in addition to pain complaint, consisted of presence of delay (3 standard deviation) of posterior tibial or fibular H-reflexes on flexion, adduction, and internal rotation (FAIR) testing, and normal paraspinal electromyographic findings. Outcome measures included visual analog scale (VAS) for pain, H-reflex delay on the FAIR test, and adverse side effects.

The primary outcome measure of the study (mean VAS score) decreased significantly in the toxin group compared to placebo at 2, 4, 6, 8,10, and 12 weeks after the toxin injection ($P < 0.0001$). FAIR test scores decreased significantly more in the toxin group compared with placebo at 2, 4, 6, and 8 weeks after injection (PT: $P = 0.038$, 0.003, 0.003, and 0.046, respectively). Adverse effects were minimal. Several open label studies have also suggested the efficacy of BoNTs in PS [11, 26, 28] (Table 13.2).

Technical Points

With the patient lying on the healthy side and the affected leg on the top with both the knee and the hip joints flexed, the point of entry of the injecting needle should be located at one centimeter below the middle of the line which connects the greater trochanter to the posterior rim of the iliac crest [27] (Fig. 13.3). A hollow,

Table 13.2 Open label clinical trials assessing the efficacy of BoNTs in piriformis syndrome

Authors and year	Type of study	# pts	Toxin	Dose	Injection	Outcome measures	Results	Side effects
Fanucci et al. (2001) [22]	Pro	30	onaA (botox)	200 u	Under CT guidance	Relief of pain caused by thigh adduction/ rotation	Pain relief noted in 26 of 30 patients (71%)	None noted
Lang A (2004) [26]	Pro	20	RimaB	5000 u	Using anatomic landmarks	50% reduction of VAS score for buttock pain	VAS score lowered at 4, 12, and16 weeks ($P < 0.05$)	Dryness of mouth
Fishman et al. (2004) [26]	Pro	20	RimaB	12,500 u	Using anatomic landmarks, 4 injection sites	50% or more decrease in VAS score	80.9% of patients met pain reduction criteria	Not mentioned
Michel et al. (2013) [11]	Pro	142	onaA	50–100 u	Anatomic landmarks	50% or more decrease in VAS score	77% of patients met pain reduction criteria	Not mentioned
Rodriguez-Pinero et al. (2017) [27]	Pro	24	IncoA	100 u	Ultrasound guidance	50% or more decrease in VAS score	At 6 months, all patients showed 50% reduction of VAS	Not mentioned
Yan et al. (2021) [28]	Ret	97	onaA versus lidocaine (1%) and bupivacaine (0.5%)	100 u	Under CT guidance, additional injection into sciatic (perineural)	VAS at 1,3, and 6 months	62% of patients that received onaA were free of pain that lasted 30 days, pain freedom in anesthetic group lasted only one day ($P = 0.005$)	None noted

Pro prospective, *Ret* retrospective, *onaA* onabotulinumtoxinA, *rimaA* rimabotulinumtoxinA, *incoA* incobotulinumtoxinA, *VAS* visual analogue scale

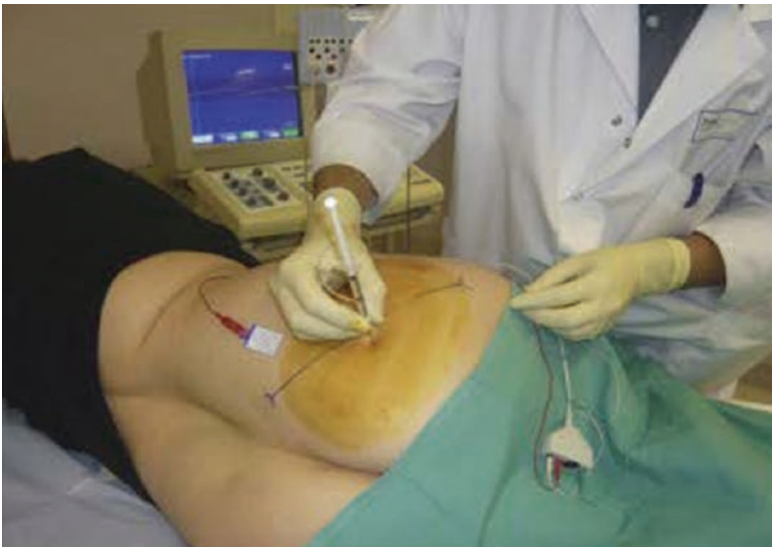

Fig. 13.3 Technique of piriformis muscle injection. (Reproduced from Michel et al. 2013 [11]. Annals of Physical Rehabilitation Medicine. With permission from publisher (Elsevier Masson SAS))

75–100 mm, dual purpose needle is used for both the EMG recording and injection. The needle is inserted deep into the muscle traversing through the gluteus maximus toward the underlying piriformis muscle. The piriformis muscle is activated by lateral rotation of the leg. After identification of the piriformis muscle by EMG, using the aforementioned approach, BoNT-A is injected into the muscle through the hollow core of the needle.

I use 100 units of onaA diluted in 1 cc of preservative-free saline and inject (under EMG guidance) half of the solution into the core of piriformis muscle and the other half an inch more superficially. The needle should be long, at least 5 in, in order to reach the piriformis muscle. In my experience, 50% of the patients with recalcitrant piriformis syndrome respond well to botulinum toxin injection. However, my experience with botulinum toxin therapy in this pain disorder is limited only to a dozen patients.

Comparator Studies

In addition to the above-cited study of Fishman et al. [23] which had a comparator arm, two other comparator studies have compared the effects of BoNT injection with steroid injections.

Porta et al. [29] compared the effect of onabotulinumetoxineA (100 units) with methylprednisolone (80 mg) in 40 subjects with myofascial pain syndrome, 23 of

whom carried the diagnosis of piriformis syndrome. Changes in the visual analog scale (VAS) were used as the primary outcome measure. On day 30, post injection, onaA reduced pain more than triamcinolone ($P = 0.06$). On day 60, post injection, onaA was significantly more effective than triamcinolone (VAS 2.3 versus 4.9, $P < 0.0001$). It is hard to determine the specific effect of onaA on pain of the patients with PS in this study since the results of the study were presented for the entire group, including 17 subjects without PS.

In an open label comparator study, Yoon et al. [30] compared the effect of abobotulinum toxinA (150 mg) with dexamethasone (5 mg mixed with 1% Novocaine) injections into the piriformis muscle in 29 patients with PS. Twenty patients received aboA and 9 received dexamethasone. The level of pain was assessed with VAS; changes in routine daily activity were evaluated by SF36 at baseline, 4, 8, and 12 weeks.

At 4, 8, and 12 weeks after injection, the mean VAS pain score was significantly lower in the subjects who received abobotulinumtoxinA compared to baseline ($P < 0001$). At 4 weeks, several subsets of SF36, general health, social function, physical function, and vitality also improved significantly in the aboA group ($P < 0.05$). On the other hand, the dexamethasone group showed no improvement and, in fact, the nine patients in this group had to be taken out of the study at 4 weeks due to continued pain, requiring other methods of pain management.

The Mechanism of Botulinum Toxin Action in Piriformis Syndrome

The analgesic effect of Botulinum toxins in pirifromis syndrome is most likely through neuromuscular and neural mechanisms. The neuromuscular mechanism is via well-known effect of BoNTs at neuromuscular junction which by deactivating the SNARE proteins blocks the release of acetylcholine from presynaptic vesicles. The resultant muscle relaxation can reduce the pressure from piriformis muscle upon the nearby sciatic nerve alleviating piriformis tension, pain, and spasms. Furthermore, intramuscular injection of botulinum toxins invariably results in reversible muscle atrophy. A decrease in the bulk of piriformis muscle can again reduce the pressure against the sciatic nerve or its branches in a tight compartment. Recent CT and MRI studies have shown presence of hypertrophied piriformis muscle in a sizeable number of patients with piriformis syndrome. In one study on PS, CT demonstrated an enlarged piriformis muscle in 45.9% of the patients [17].

In recent years, a growing body of literature indicates that the analgesic effects of BoNTs after intramuscular injection are mostly related to their direct effect upon the peripheral nerve terminals and peripheral neurons. In the case of BoNT-A, the injected toxin is capable of reducing the peripheral action of major pain transmitters, namely, calcitonin gene-related peptide (CGRP), substance P (SP), and glutamate [31, 32]. It has been shown that cleaved SNAP 25 (protein target of BoNTA)

travels from periphery to dorsal root ganglion (DRG) and there is ample evidence that it blocks the release of pain transmitters from DRG neurons [33, 34]. Similar observations have been reported in DRG and trigeminal cell cultures [35, 36]. Additionally, several investigators have shown evidence for central action of type A and type B toxins after intramuscular or subcutaneous injection in both animals and in human subjects [37–39].

In recalcitrant piriformis syndrome, like any chronic pain condition, the maintenance of pain is the result of peripheral and central sensitization of the sensory neurons [40]. After peripheral injection, botulinum toxins A and B can specifically reduce the release of substance P and cFos activation in spinal neurons [33, 41]. Finally, when central sensitization develops, the wide range action neurons of the spinal cord start perceiving non-nociceptive peripheral stimuli as nociceptive leading to enhancement of pain perception [42]. One of the major non-nociceptive inputs to the central nervous system comes from the intrafusal muscle fibers (muscle spindles) that constantly report the length of the muscle to the spinal neurons. It has been shown that intramuscular injection of botulinumtoxinA leads to marked suppression of intrafusal muscle fiber discharges [43, 44].

Conclusion

The data from blinded and open label studies demonstrate that BoNT injections into piriformis muscle are safe and able to alleviate pain in recalcitrant piriformis syndrome. Using the efficacy criteria set forth by the guideline and development subcommittee of the America Academy of Neurology [45, 46], based on the current literature, the level of efficacy is B (probably effective) due to availability of three class II studies [23–25]; an A efficacy level needs two class I studies. Comparator studies have shown that injection of BoNT-As (onaA and aboA) into the piriformis muscle induces better and longer pain relief than steroid injections.

In recent years, the technique of injection has improved by better identification of the piriformis muscle through the use of ultrasound and more refined CT and MRI techniques [47]. The toxin's effective minimum dose for treatment of PS is a matter of debate, and an optimal dose of the botulinum neurotoxin for relieving the pain in PS remains to be established. In the case of BoNTA's dose, in agreement with other investigators [24, 27, 28], we used 100 units of onaA, whereas Fishman et al. [23, 25] have used higher doses (200 units of onaA and 300 units of incoA). One group of investigators, in an open label study [30], claimed success with low toxin dose that is 150 units of aboA (roughly comparable to 50–70 units of onaA). Establishment of efficacy and defining the minimum effective dose of BoNTs in PS requires conducting a randomized, double-blind, multicenter clinical trial on a large cohort of patients with piriformis syndrome.

References

1. Yeoman W. The relation of arthritis of the sacro-iliac joint to sciatica: with one analysis of 100 cases. Lancet. 1928;2:1119–23.
2. Robinson DR. Piriformis syndrome in relation to sciatic pain. Am J Surg. 1947;73:355–8.
3. Stewart JD. The piriformis syndrome is overdiagnosed. Muscle Nerve. 2003;28:644–6.
4. Tiel RL. Piriformis and related entrapment syndromes: myth and fallacy. Neurosurg Clin N Am. 2008;19:623–7.
5. Hallin RP. Sciatic pain and the piriformis muscle. Postgrad Med. 1983;74:69–72.
6. Hopayian K, Song F, Riera R, Sambandan S. The clinical features of the piriformis syndrome: a systematic review. Eur Spine J. 2010;19:2095–109. https://doi.org/10.1007/s00586-010-1504-9.
7. Miller TA, White KP, Ross DC. The diagnosis and management of piriformis syndrome: myths and facts. Can J Neurol Sci. 2012;39:577–83.
8. Probst D, Stout A, Hunt D. Piriformis syndrome: a narrative review of the anatomy, diagnosis, and treatment. PM R. 2019;11(Suppl 1):S54–63. https://doi.org/10.1002/pmrj.12189.
9. Durrani Z, Winnie AP. Piriformis muscle syndrome: an underdiagnosed cause of sciatica. J Pain Symptom Manag. 1991;6:374–9.
10. Kirschner JS, Foye PM, Cole JL. Piriformis syndrome, diagnosis and treatment. Muscle Nerve. 2009;40:10–8.
11. Michel F, Decavel P, Toussirot E, Tatu L, Aleton E, Monnier G, Garbuio P, Parratte B. Piriformis muscle syndrome: diagnostic criteria and treatment of a monocentric series of 250 patients. Ann Phys Rehabil Med. 2013;56:371–83.
12. Jankovic D, Peng P, van Zundert A. Brief review: piriformis syndrome: etiology, diagnosis, and management. Can J Anaesth. 2013;60:1003–12.
13. Fishman LM, Dombi GW, Michaelsen C, et al. Piriformis syndrome: diagnosis, treatment, and outcome – a 10-year study. Arch Phys Med Rehabil. 2002;83:295–301.
14. Campbell WW, Landau ME. Controversial entrapment neuropathies. Neurosurg Clin N Am. 2008;19:597–608.
15. Rodrigue T, Hardy RW. Diagnosis and treatment of piriformis syndrome. Neurosurg Clin N Am. 2001;12:311–9.
16. Natsis K, Totlis T, Konstantinidis GA, Paraskevas G, Piagkou M, Koebke J. Anatomical variations between the sciatic nerve and the piriformis muscle: a contribution to surgical anatomy in piriformis syndrome. Surg Radiol Anat. 2013.
17. Vassalou EE, Katonis P, Karantanas AH. Piriformis muscle syndrome: a cross-sectional imaging study in 116 patients and evaluation of therapeutic outcome. Eur Radiol. 2018;28(2):447–58. https://doi.org/10.1007/s00330-017-4982-x.
18. Vij N, Kiernan H, Bisht R, Singleton I, Cornett EM, Kaye AD, Imani F, Varrassi G, Pourbahri M, Viswanath O, Urits I. Surgical and non-surgical treatment options for piriformis syndrome: a literature review. Anesth Pain Med. 2021;11(1):e112825. https://doi.org/10.5812/aapm.112825.
19. Gulledge BM, Marcellin-Little DJ, Levine D, Tillman L, Harrysson OL, Osborne JA, Baxter B. Comparison of two stretching methods and optimization of stretching protocol for the piriformis muscle. Med Eng Phys. 2014;36:212–8.
20. Cox J, Varatharajan S, Côté P. Optima collaboration. Effectiveness of acupuncture therapies to manage musculoskeletal disorders of the extremities: a systematic review. J Orthop Sports Phys Ther. 2016;46(6):409–29. https://doi.org/10.2519/jospt.2016.6270.
21. Tabatabaiee A, Takamjani IE, Sarrafzadeh J, Salehi R, Ahmadi M. Ultrasound-guided dry needling decreases pain in patients with piriformis syndrome. Muscle Nerve. 2019;60(5):558–65. https://doi.org/10.1002/mus.26671.
22. Fanucci E, Masala S, Sodani G, Varruciu V, Romagnoli A, Squillaci E, et al. CT-guided injection of botulinic toxin for percutaneous therapy of piriformis muscle syndrome with preliminary MRI results about denervative process. Eur Radiol. 2001;11:2543–8.

23. Fishman LM, Anderson C, Rosner B. BOTOX and physical therapy in the treatment of piriformis syndrome. Am J Phys Med Rehabil. 2002;81(12):936–42. https://doi.org/10.1097/00002060-200212000-00009.
24. Childers MK, Wilson DJ, Gnatz SM, Conway RR, Sherman AK, Childers MK, Wilson DJ, Gnatz SM, Conway RR, Sherman AK. Botulinum toxin type A use in piriformis muscle syndrome: a pilot study. Am J Phys Med Rehabil. 2002;81:751–9.
25. Fishman LM, Wilkins AN, Rosner B. Electrophysiologically identified piriformis syndrome is successfully treated with incobotulinum toxin a and physical therapy. Muscle Nerve. 2017;56(2):258–63. https://doi.org/10.1002/mus.25504.
26. Lang AM. Botulinum toxin type B in piriformis syndrome. Am J Phys Med Rehabil. 2004;83(3):198–202. https://doi.org/10.1097/01.phm.0000113404.35647.d8.
27. Rodríguez-Piñero M, Vidal Vargas V, Jiménez Sarmiento AS. Long-term efficacy of ultrasound-guided injection of incobotulinumtoxinA in piriformis syndrome. Pain Med. 2018;19(2):408–11. https://doi.org/10.1093/pm/pnx135.
28. Yan K, Xi Y, Hlis R, Chhabra A. Piriformis syndrome: pain response outcomes following CT-guided injection and incremental value of botulinum toxin injection. Diagn Interv Radiol. 2021;27(1):126–33. https://doi.org/10.5152/dir.2020.19444.
29. Porta MA. Comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. Pain. 2000;85:101–5.
30. Yoon SJ, Ho J, Kang HY, Lee SH, Kim KI, Shin WG, Oh JM. Low-dose botulinum toxin type A for the treatment of refractory piriformis syndrome. Pharmacotherapy. 2007;27:657–65.
31. Rapp DE, Turk KW, Bales GT, Cook SP. Botulinum toxin type a inhibits calcitonin gene-related peptide release from isolated rat bladder. J Urol. 2006;175(3 Pt 1):1138–42. https://doi.org/10.1016/S0022-5347(05)00322-8.
32. Hou YP, Zhang YP, Song YF, Zhu CM, Wang YC, Xie GL. Botulinum toxin type A inhibits rat pyloric myoelectrical activity and substance P release in vivo. Can J Physiol Pharmacol. 2007;85(2):209–14. https://doi.org/10.1139/y07-018.
33. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155(4):674–84. https://doi.org/10.1016/j.pain.2013.12.009.
34. Fan C, Chu X, Wang L, Shi H, Li T. Botulinum toxin type A reduces TRPV1 expression in the dorsal root ganglion in rats with adjuvant-arthritis pain. Toxicon. 2017;133:116–22. https://doi.org/10.1016/j.toxicon.2017.05.001.
35. Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. Toxicon. 2000;38(2):245–58. https://doi.org/10.1016/s0041-0101(99)00153-1.
36. Durham PL, Cady R, Cady R. Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache. 2004;44(1):35–42; discussion 42–3. https://doi.org/10.1111/j.1526-4610.2004.04007.x.
37. Mazzocchio R, Caleo M. More than at the neuromuscular synapse: actions of botulinum neurotoxin A in the central nervous system. Neuroscientist. 2015;21(1):44–61. https://doi.org/10.1177/1073858414524633.
38. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459.
39. Lacković Z. Botulinum toxin and pain. Handb Exp Pharmacol. 2021;263:251–64. https://doi.org/10.1007/164_2019_348.
40. Aoki KR, Francis J. Updates on the antinociceptive mechanism hypothesis of botulinum toxin A. Parkinsonism Relat Disord. 2011;17(Suppl 1):S28–33. https://doi.org/10.1016/j.parkreldis.2011.06.013.
41. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012;61(2):236–9. https://doi.org/10.1016/j.neuint.2012.05.001.

42. Roberts WJ, Foglesong ME. Spinal recordings suggest that wide-dynamic-range neurons mediate sympathetically maintained pain. Pain. 1988;34(3):289–304. https://doi.org/10.1016/0304-3959(88)90125-X.
43. 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. https://doi.org/10.3109/00016489309135834.
44. Jang DH, Sung IY. Response: botulinum toxin induces chemodenervation of intrafusal and extrafusal fibers. J Child Neurol. 2013;28(6):820. https://doi.org/10.1177/0883073813487026.
45. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology. 2008;71(20):1639–43. https://doi.org/10.1212/01.wnl.0000336535.27773.c0.
46. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008;71(20):1634–8. https://doi.org/10.1212/01.wnl.0000336533.19610.1b.
47. Filippiadis D, Gkizas C, Velonakis G, Flevas DA, Kokkalis ZT, Mavrogenis AF, Mazioti A, Brountzos E, Kelekis N, Kelekis A. Computed tomography-guided percutaneous infiltrations for piriformis syndrome: a single-center retrospective study. J Long-Term Eff Med Implants. 2020;30(2):113–8. https://doi.org/10.1615/JLongTermEffMedImplants.2020035543.

Chapter 14
Botulinum Toxin Therapy for Prevention of Postsurgical Pain

Introduction

Following a number of surgical procedures, the muscles affected by surgery may contract and cause local muscle spasms and pain. In 20–40% of the affected patients, pain can be severe and responds poorly to analgesic medications [1]. A growing body of literature strongly suggests that injection of BoNT into the involved muscles before the intended surgical procedure can reduce and sometimes prevent postsurgical pain. Alleviation and prevention of postsurgical pain is obviously of significant importance to the patient.

Postmastectomy Breast Reconstruction

After mastectomy, many patients develop anxiety and depression arising from the perception of distorted body image and loss of femininity [2, 3]. In Denmark, approximately 20% of women choose to have breast reconstruction after breast cancer surgery, and this number is increasing [4]. Several studies have shown that breast reconstruction after mastectomy can restore patients' healthy body image and improve mental health and quality of life [5, 6].

Implant-based breast reconstruction is now the most common breast reconstructive technique performed after mastectomy [7]. It is a staged procedure during which, first, the surgeon imbeds an expander deep into the pectoral muscle followed by insertion of breast implants. The procedure may take weeks or even months. Unfortunately, during the expansion phase, many patients suffer from spasms of pectoralis muscle leading to severe pain. In some patients, spasms of pectoralis muscle may be quite severe and debilitating [8, 9] and lead to premature removal of the expander [10]. Muscle hypoxia during the expanding procedure can be a

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_14

causative factor as well. The hypoxic muscle fibers may undergo degeneration and fibrosis [11]. Recalcitrant and continuous pain after reconstructive surgery may require special procedures such as bilateral pectoral neurectomies [12, 13].

Breast reconstruction is the most common reconstruction surgery performed among cancers mounting to over 100,000 procedures each ear [14]. Commonly used nonopioid drugs used for prevention and alleviating pain associated with reconstruction/expansion surgery include acetaminophen and celecoxib. Many surgeons prescribe opioid analgesics pre-emptively in anticipation of postoperative pain [15]. Among opioid medications, oxycodone (5 mg tablets) is most commonly used. Opioid dependency, however, is a major issue and can develop in as high as 7% among cancer patients [16]. The type of breast reconstruction may also influence postoperative pain. In one study, prepectoral breast reconstruction was associated with less postoperative pain and opioid intake compared to postpectoral reconstruction surgery [17]. Local infusion of anesthetic bupivacaine into mastectomy skin flaps and serratus fascia [18] or continuous infusion of bupivacaine under the implant have been also used for reducing pain following postmastectomy reconstructive surgery. Pacik et al. [19], using the latter approach, reported that 78% of the 644 consecutively studied patients experienced decreased pain in the morning after surgery before implant mobility exercises. More recently, the intrapectoral block of the lateral and medial pectoral nerves has been introduced to avoid the use of opioids for pain relief after breast reconstructive surgery. The procedure can be performed by an anesthesiologist under ultrasound guidance. A single dose of 5–10 ml of 0.5% bupivacaine hydrochloride diluted 1:1 with saline is infused between the pectoralis major and minor muscles in one spot at the time of surgery (Fig. 14.1). Scheflan et al., using this technique, succeeded in avoiding the use of opioids in 350 patients who underwent reconstructive breast surgery [20].

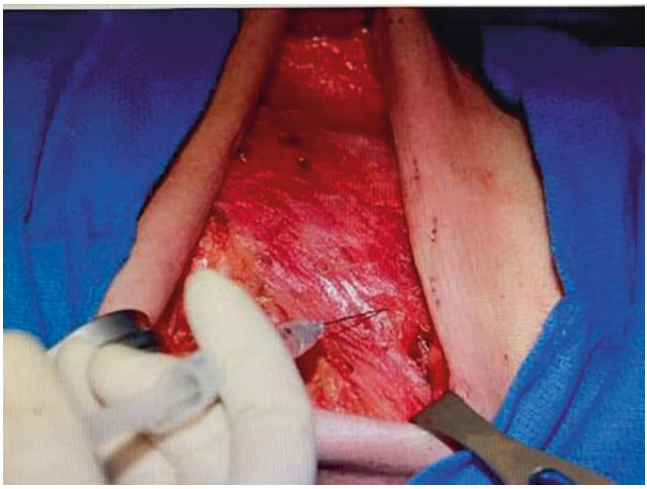

Fig. 14.1 Technique of injection into pectoralis muscles. From Gabriel and Maxwell. Use of botulinum toxinA in postmastectomy breast reconstruction. (Reprinted from Botulinum toxinA treatment in surgery, dentistry, and veterinary medicine. Jabbari B(ed). 2020. PP. 187–193. With permission from Springer Nature)

Botulinum Toxin Treatment of Pain After Breast Reconstructive Surgery

Intramuscular or subcutaneous injection of Botulinum neurotoxins (BoNT) can reduce pain via several mechanisms by reducing the release of pain transmitters (glutamate, calcitonin gene-related peptide, substance P) at the peripheral terminal and central synapses [21–34]. In human, their efficacy in reducing pain has been shown in several pain syndromes [35–44].

In 2014, Winocuor et al. [45] reviewed and reported the literature regarding the use of botulinum toxins for prevention or treatment of postmastectomy pain. They cited a total of eight studies in which injection of the neurotoxin was used for pain prevention. Most studies were considered weak with a rating of <5 in New Castle Ottawa Scale (NCOS, 0–8). Only the study of Layeeque et al. [46] was given a rating of 7 (on NCOS scale) for having a good design despite being a nonblinded study. The utilized dose of the toxin was comparable between different studies, and the investigators found injection of BoNTs intraoperatively helpful in preventing postmastectomy pain.

Layeeque et al. [46] conducted a prospective, randomized study in 48 patients who were undergoing mastectomy, followed by placement of expander. Twenty-two patients received onabotulinumtoxinA (onaA) and 26 did not. The groups were comparable in terms of age, tumor size, and expander size. In the onaA group, 100 units of toxin were diluted with 40–60 cc of saline and injected at four sites into the pectoralis muscle before surgery (Fig. 14.1). Pain was evaluated through visual analog scale (VAS) (0–10). The group that received onaA experienced less pain shortly after surgery and during expansion procedures ($P < 0.0001$ and $P < 0.009$). A number of other parameters also improved including shorter hospital stay and the dose of morphine required during hospital stay for pain control. No side effects were reported.

Between 2015 and 2021, three double-blind, placebo -controlled studies have been published on the subject of BoNT therapy for postbreast reconstruction surgery pain.

In 2015, Lo and Aycock [47] published the results of a blinded and placebo-controlled study on 23 women who had bilateral mastectomy and reconstructive surgery with expanders. All patients had bilateral subcutaneous bupivacaine pumps for pain control. Patients were injected intraoperatively with 100 units of onabotulinumtoxinA diluted in 10 ml of normal saline into the pectoralis muscles of one side and with normal saline into the pectoralis of the other side. The toxin or saline was delivered into the muscle in a fanlike fashion. The pain change between two sides was compared using a 0–10 numerical Visual Analogue Scale (VAS) at post-operative day 1, and then weekly for 12 weeks. Both toxin and saline reduced pain significantly at days 1, 7, and 14 post-operatively. The difference between the two, however, was not statistically significant.

In the same year, Gabriel et al. [48] reported on 30 patients following mastectomies with immediate expander/ADM reconstruction. The patients were divided into two groups. One group of 15 patients received 40 units of onabotulinumtoxinA (Botox-allergan) into each pectoralis major muscle intraoperatively through four

serial injections (Fig. 14.1). The placebo group of 15 patients received four serial injections of normal saline. The two groups were studied blindly. There was no significant difference between the two groups regarding age, expander size, laterality, and complications. The level of pain was measured by the visual analogue scale (VAS) with scores ranging from 0 to 10. The primary outcome was the change from the baseline of pain score. The secondary outcome was the amount of narcotics used during postoperative days, 1–3 and 3–45. The mean VAS score of the toxin group demonstrated significant pain reduction compared to placebo from day 7 to day 45 ($P < 0.0001$). There was also a significant decrease in narcotic use in the toxin group noted between days 7–45 ($P < 0.0001$).

In 2020, Lemaine et al. [49] reported the results of a third double-blind, placebo-controlled study on this subject. The authors studied 131 patients with breast reconstructive surgery and tissue expander placement of whom 52% received toxin injection and 48% received placebo. In the toxin group, 100 units of onabotulinumtoxinA (Botox) were injected during surgery retrogradely into the pectoralis major muscle using a single injection. The pain intensity was measured by VAS and the patients' well-being by the BREAST-Q scale. The authors found no significant difference between the toxin and placebo group in regard to changes of VAS and BREAST-Q. For both groups, the change in the VAS score was identical.

Comment

Pain after breast reconstructive surgery with expander implant is a challenging issue for the breast surgeons. Although, a well-designed, open label prospective study with control group demonstrated statistically significant pain relief after BoNT injection into pectoralis muscle, the double-blind, placebo-controlled studies have been contradictory. Only one of the three studies [48] reported significant pain relief after BoNT injection. A close scrutiny of the reported data, however, reveals significant differences in the design of the three studies. The two studies that reported negative results [47, 49] had high placebo effects; in fact, in one study, pain improvement in the placebo group was identical to that of the toxin group. Such high placebo effects practically invalidated the reported negative efficacy results.

If one takes the positive result of the one study that had no significant placebo effect [48], at present, the level of efficacy of onabotulinumtoxinA in relief of postreconstruction breast surgery would be B (probably effective, based on the efficacy guidelines of AAN) [50, 51]. Larger, controlled studies are needed to define the role of pectoralis muscle injection with BoNTs in reduction of pain that develops after insertion of expanders following reconstructive breast surgery.

Posthemorrhoidectomy Pain

Hemorrhoid is one of the most common forms of human ailments with a prevalence of 4–36% [52]. Men and women are equally affected. The prevalence increases with age from the beginning of adulthood until the seventh decade and declines thereafter. More individuals are affected in the higher socioeconomic groups and among Caucasians and Jews [53]. Hemorrhoidectomy ranks among the most common procedures in the United States and Europe with an annual rate of 60 and 46 per 100,000 individuals reported in the United States and France, respectively [54, 55].

Postsurgical pain after hemorrhoidectomy is common and can be severe and exhausting [56]. The pain can occur at rest or during defecation and is generally attributed to spasms of the internal anal sphincter.

Treatment of Posthemorrhoidectomy Pain

A diet that softens the stools, and intermittent sitz baths offer some relief. Pharmacological therapy includes the use of acetaminophen, nonsteroidal, anti-inflammatory analgesic drugs, muscle relaxants, and opioids. Blinded and placebo-controlled studies have shown partial efficacy for certain forms of topical ointments. Glyceryl trinitryte (GTN) ointment (0.2%) is now commonly used for treatment of posthemorrhoidectomy pain based on controlled investigations [57–59]. In one study [60], a combination of Gyceryl trinitrate ointment with lignocaine (lighnocaine 2% and GTN 0.2%) has been found more effective than either treatment alone. Calcium channel blocker (CCB) ointments also have shown efficacy against posthemorrhoidectomy pain in two-blinded, placebo-controlled studies [61, 62]. In both studies (one using diltiazem and the other nifidipine), the pain was considerably less at 7 days postsurgery in patients taking CCB compared to the placebo group ($P < 0.05$). A recent review with meta-analysis of the data from four randomized clinical trials (total of 57 patients) revealed that metronidazole can reduce posthemorrhoidectomy pain [63]. Four of three studies, however, had some degree of bias. Metronidazole, through its antimicrobial and antioxidant effects, promotes wound healing [64, 65].

In the case of persistent pain, other measures which have shown some efficacy in blinded studies may be employed. These consist of local anesthetic infiltration [66], anesthetic regional blockage [67], transdermal fentanyl [68], and diathermy excision [69]. More details on various approaches to manage posthemorrhoidectomy pain can be found in comprehensive reviews of this subject [70–72].

Botulinum Toxin Treatment of Posthemorrhoidectomy Pain

The vast literature on the analgesic effect of BoNT injections [22–44] encouraged the colo-rectal specialist to investigate the efficacy of BoNT injections in relieving posthemorrhoidectomy pain. To date, four randomized, double-blind, placebo-controlled studies have been reported on this subject. There is also one randomized controlled study, and one prospective comparator study.

Blinded, Placebo Controlled Studies

Davies et al. [73] conducted a double-blind, placebo-controlled study on 50 consecutive patients who were undergoing Milligan-Morgan hemorrhoidectomy. OnabotulinumtoxinA or saline was injected intraoperatively at two points (0.2 cc per site) into the posterior midline of the internal anal sphincter via a 27-gauge needle. In the case of onaA, the preparation consisted of 50 units in 1 cc of saline, hence 0.4 cc of the solution contained 20 units of the toxin. At the end of the procedure, both groups were injected with 20 ml of bupivacaine (0.25%) into the perianal skin. Patients were also prescribed a seven-day supply of cocodomal 30/500 (codeine phosphate 30 mg, paracetamol 500 mg, 4 times per day orally) and instructed to use it as required. Pain was assessed by visual analog scale/VAS (0–10) at baseline and then daily via a questionnaire for the 7 days following the procedure. The mean pain score at postoperative days 6 and 7 was significantly lower in the patients who had onaA injections ($P < 0.05$). No side effects were reported.

In another blinded and placebo-controlled study of 30 patients, the effect of BoNT-A versus saline was investigated during peri- and posthemorrhoidectomy symptoms including pain [74]. Patients had grades III and IV hemorrhoids. In the toxin group, the solution was prepared by adding 2 cc saline to the onaA vial of 100 units (50 units/cc). Then 0.4 cc (20 units) was injected into the anterior midline of the anal sphincter at two points. The control group received the same volume of saline. Patients were assessed at baseline and then daily for 30 days.

The postoperative pain measured by VAS was significantly lower in the onaA group compared to the placebo during the first 7 days ($P = 0.001$). Subsequently, patients in the placebo group used a larger number of analgesic tablets compared to the onaA (22.3 ± 5.1 vs. 14.8 ± 6.2; $P < 0.05$). In the placebo group, the manometric anorectal resting pressure (MRP) was significantly raised ($P < 0.05$) on the fifth postoperative day, whereas it was significantly reduced ($P < 0.01$) in the onaA group. The length of wound healing was 23.8 ± 4.1 days in the onaA group compared to 31.3 ± 5.5 days in the placebo group ($P < 0.05$). The same investigators [75] found very similar positive findings in another double-blind study which assessed efficacy of intrasphincteral injection of onaA in relieving the pain of inoperable, thrombosed hemorrhoids. The type of toxin, dose, and technique of injection were identical to their postsurgical study.

In contrast to the three abovementioned studies on posthemorrhoidectomy pain, a fourth placebo-controlled study of 32 patients with grades III and IV hemorrhoids found no improvement of postoperative pain and no change in RMP after injection of BoNT-A into the intersphincteric space [76]. The BoNT-A group, however, demonstrated significantly lower squeeze resting pressure ($P < 0.05$) compared to the placebo. The authors used 150 units of abobotulinumtoxinA diluted in 0.5 cc of saline in this study. Pain and MRP were assessed over 14 days (13 and 13 patients in each group).

Randomized, Controlled Study

Recently, the effect of intersphincteric BoNT-A injection on posthemorrhoidectomy pain was investigated in a randomized controlled study of 88 patients (44 toxin and 44 control) [77]. In the toxin group, patients were injected (immediately after resection, before closing the wound) with 0.5 ml of a solution containing 30 units of onabotulinumtoxinA (Botox-Allergan). During the postoperative period, all patients (in both groups) received two oral antibiotics (metronidazole 400 mg, three times a day and norfloxacin 400 mg, twice a day) and diclofenac 25 mg oral three times a day for 1 week. The primary outcome was changes in pain, assessed by VAS. VAS score both at 12 h and 24 h after surgery was significantly lower in the toxin group compared to the control group (at 12 h: 4.435 ± 2.149 vs 6.232 ± 2.307, $P < 0.001$; at 24 h: 2.205 ± 2.079 vs 3.744 ± 2.361, $P = 0.003$). The toxin group had also a shorter time in defecation without pain compared to the control group ($p = 0.007$). There was no difference in immediate and delay complications between the two groups.

Prospective, Randomized Comparator Studies

Patti et al. [78] evaluated the efficacy of onabotulinumtoxinA versus topical Glyceryl Trinitrate (GT) ointment in 30 patients with grades III and IV hemorrhoids undergoing hemorrhoidectomy. In the toxin group, each patient received a total of 20 units (two injections, each 10 units) into anterior midline of anal sphincter. The dilution was 50 units/cc of saline, hence, 20 units /0.4 cc. The other group used topical GT (300 mg) three times daily for 30 days. The postsurgical pain (assessed by VAS), the duration of wound healing, and anorectal manometry were evaluated before and after hemorrhoidectomy. The onaA group demonstrated significant pain relief at rest, but not during defecation ($P = 0.01$, observed up to 7 days). Patients in the GT group used a larger number of analgesic tablets compared with the onaA group (20.4 T 6.1 vs. 16.8 GT 5.3; $P < 0.05$). The maximum resting pressure (MRP) was also decreased in the toxin group at both days 5 and 40 ($P < 0.0001$) postoperatively. The wound healing duration was shorter in the onaA group, but the difference did

not reach statistical significance. The authors concluded that a single injection of BoNT-A improved pain and reduced anorectal pressure significantly compared to 1 month of GT treatment.

Comment

The literature on the efficacy of onabotulinumtoxinA in reducing posthemorrhoidectomy pain contains four double-blind, placebo-controlled, class II studies three of which [73–75] demonstrated the preventive value of BoNT injections in reducing postoperative pain. Furthermore, one Class II comparator study also reports the efficacy of onaA against this form of pain when compared with topical Glyceryl Trinitrate (GT) [78]. The positive effect of onabotulinumtoxinA in this area is also supported by a randomized, controlled study [77]. The one negative report on the efficacy of abobotulinumtoxinA for preventing posthemorrhoidectomy pain [76] is at odds with these positive observations. The injected dose of aboA (150 units) in this study cannot explain the failure of the toxin (aboA) since in clinical trials a 2.5–3 unit/1unit (aboA/onaA) is often used. One explanation for the negative result of this particular study may be the difference between the employed techniques. A more plausible explanation is that results of this study show a large placebo effect as the mean of maximum pain score improved notably for both toxin and placebo around days 10–12. When the number of studied patients is small and both drug and placebo show similar degree of improvements of a measured outcome, the results do not necessarily negate the efficacy of the drug. If we take into account the blinded studies that did not show a large placebo effect [73–75], the level of efficacy of onabotulinumtoxinA in relieving posthemorrhoidectomy pain would be B (probably effective) based on availability of two or more class II studies (according to the efficacy criteria set forth by the Guideline and Assessment Subcommittee of the American Academy of Neurology [50, 51]. More blinded studies are necessary to discern the efficacy of BoNT injections for this important form of postsurgical pain.

Prevention and Reduction of Posthernia Repair Pain

Incisional hernia repair (IHR) is often associated with severe postoperative pain which could affect quality of life, the length of hospital stay, and ultimately return to full activity at work. In one study, the average VAS pain score for the first 14 days after hernia repair was 6.1, and in some patients, the severe postoperative pain lasted well beyond 14 days [79].

Botulinum toxin injections are now used by some surgeons during abdominal wall reconstruction surgery to gain fascial domain and improve rates of fascial closure [80–88]. The preliminary studies have shown that BoNT injections can relieve

postsurgical pain and reduce consumption of opioids after hernia and abdominal repair surgery.

Zendejas et al. [89] hypothesized that injection of botulinum neurotoxins into the abdominal muscles before surgery can improve hernia repair and reduce postsurgical care through muscle relaxation. The authors compared postoperative pain, opioid requirement, procedure complications with controls in 88 patients (22 toxin, 66 controls) who underwent incisional hernia repair. Pain was assessed by the visual analog scale (VAS) (0–10). Patients and controls were matched for age, body mass index, and the type of repair. OnabotulinumtoxinA (onaA) was injected into the transverse abdominalis and internal and external oblique muscles under ultrasonic guidance during conscious sedation. The total dose of the toxin was 300 units diluted in 150 cc of normal saline.

Patients who were injected with onaA reported less pain on hospital day (HD) 2 (5.2 ± 1.5 vs. 6.8 ± 2 for control group) and HD4 (3.6 ± 1.2 vs. 5.2 ± 1.9): all $p < 0.007$. Also, the group that received onaA injection required significantly less opioid analgesia (mean ± SD morphine equivalents) when compared to controls on hospital day (HD) 2 and 5, HD2 48 ± 27 versus 87 ± 41; HD5, 17 ± 16 versus 48 ± 45. There was no difference in postoperative complications affecting the surgical site (9% vs. 14%), opioid-related adverse events (5% vs 5%), hospital stay (4 ± 3 vs 3 ± 2 days), or hernia recurrence at 18 months mean follow-up (9% vs 9%).

Blaha et al. [90] studied the effect of botulinumtoxinA (Botox) on the amount of opioid use for pain relief after hernia surgery. The authors compared the amount of opioid use after hernia surgery in 22 patients in the toxin group with 19 patients in the nontoxin group. The total dose of injected onaA was 200 units distributed into the following muscles: left and right rectus abdominalis, as well as left and right oblique and transverse abdominalis muscles. Among different factors studied, stepwise linear regression analysis identified use of onaA injection as the only predictor of morphine milligram equivalents (MME) usage ($P = 0.48$).

Reduction of Severe Pain After Adductor Release Surgery

Adductor release surgery is an established procedure which can prevent hip dislocation in children with adductor spasticity and cerebral palsy (CP) [91]. The procedure is effective, but in many children, postoperative spasm of adductor muscles develops after surgery causing severe pain.

Barnwood et al. [92] conducted a prospective, randomized, double-blind study in 16 children with CP and spasticity who were undergoing adductor release surgery. The children were diplegic or quadriplegic with a mean age of 4.7 years. The surgery was performed in order to prevent hip subluxation. The authors used onabotulinumtoxinA (onaA), Allergan Inc., prepared as 10 units/0.1 cc of saline. Each adductor muscle was injected at two sites (2 units/kg per site) for a total dose of 8 units/kg, 5–10 days before surgery (Fig. 14.2). The injector identified the injection site by palpating the pubic tubercle and adductor longus tendon, while hips were

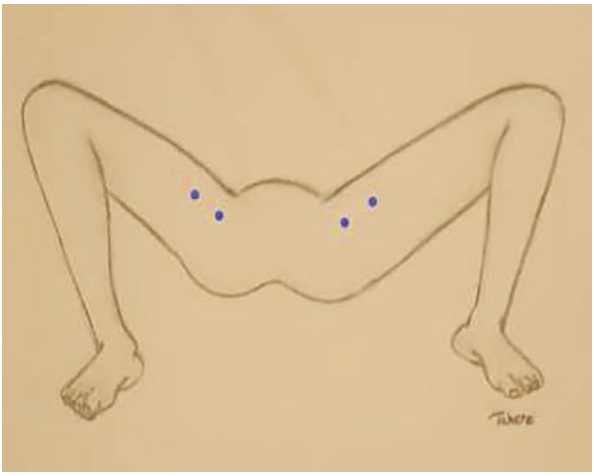

Fig. 14.2 Site of adductor injection to prevent pain after adductor release surgery according to Barnwood et al., 2000 [92]. (Drawing courtesy of Tahere Moussavi, MD)

held in abduction and flexion. Injections were performed at two sites into the adductor muscle of the thigh approximately, 2 cm and 4 cm from the pubic tubercle and 1 cm posterior to the adductor longus tendon.

The surgery comprised lengthening of adductor longus and gracilis, as well as lengthening of adductor brevis partially or completely until 30–40 ° of hip abduction in flexion was obtained to a combined abduction range of 60–80 °. In order to obtain a symmetrical range of abduction, hips with asymmetric abduction range were managed by asymmetric surgery.

The mean pain score in the onaA group showed a reduction of 74% ($P < 0.003$) and patients analgesic requirement dropped by approximately 50% ($P < 0.005$). The onaA group also had significantly shorter length of hospital stay with 33% reduction in length of stay ($P < 0.003$). The patients in the onaA group did considerably better in respect to postoperative care, reduction of analgesic requirement, and shortening the length of hospital stay.

Botulinum Toxin Injection of Sphincter of Oddi for Postcholecystectomy Pain.

After cholecystectomy, increased pressure in the biliary duct leads to postcholecystectomy biliary pain in a sizeable number of patients. Increased pressure in the duct also carries 3–31% danger of pancreatitis [93, 94]. Persistent pain associated with increased pressure in the biliary duct after cholecystectomy is often treated with Oddi sphincterectomy [95].

One prospective, open label study and one retrospective chart audit study have reported significant improvement of postcholecystectomy pain after administration of onabotulinumtoxinA into the Oddi sphincter. Furthermore, both studies claim a predictive value for botulinum toxin therapy since patients who responded well to BoNT therapy were more likely to respond well to endoscopic sphinctrectomy.

Wehrmann et al. [96] (1998) enrolled 22 patients with a history of cholecystectomy and postcholecystectomy pain and monometrically confirmed sphincter of Oddi dysfunction (SOD) in a 3-year prospective study. All patients received injections of onabotulinumtoxinA into the ampulla of Vater, a total of 100 units at one site. After onaA treatment, manometrric pressure returned to normal in all patients. Twelve of 22 patients (55%) became pain free. Pain returned in 6 months, however. Subsequent endoscopic sphincterectomy relieved pain in 11 of 12 patients (91%) who had responded to onaA, but in only 2 of 10 patients (20%) who had not responded to onaA ($P < 0.01$). The authors concluded that not only onabotulinumtoxinA relieves postcholectomy pain in a sizeable number of patients, it also can predict who will later respond to endoscopic sphincterectomy. One patient in this study developed mild pancreatitis.

The conclusion of the aforementioned study is supported by a retrospective chart audit of 64 patients with postcholestectomy pain (4 episodes or more per month) who received onaA injection (100 units) into the sphincter of Oddi for pain relief [97]. Of the 64 patients, 46 (72%) had experienced at least four pain-free weeks after onaA treatment and 44 of 46 (96%) had experienced pain relief following endoscopic sphincterectomy. Every patient with increased manometric pressure who also had at least 4 weeks of pain relief following onaA injection of sphincter of Oddi experienced pain relief following endoscopic sphincterotomy. No patient had any side effect after BoNT injection. The investigators came to the same conclusion that injection of onaA into the sphincter of Oddi improves postcholecystectomy pain and has predictive value as to the outcome of subsequent endoscopic sphincterectomy.

Murray [98] reported on the analgesic effect of BoNT injection into sphincter of Oddi in the absence of biliary calculus. In the absence of biliary calculus, biliary pain can be the result of gall bladder dyskinesia or biliary sphincter of Oddi hypertension [93]. Murray retrospectively reviewed the result of 100 units of onabotulinumtoxinA (Botox) injection into sphincter of Oddi of 25 patients who had biliary pain in the absence of biliary stone [99]. Eleven patients, after onaA injection, had temporary pain relief; 10 accepted to have endoscopic sphincterotomy (ES). All 10 had total pain relief after the procedure. Of the 14 patients who did not respond to onaA injection, 10 patients accepted to also have ES; eight of these patients experienced total pain relief. The author concluded that botulinum toxin relaxation of sphincter of Oddi helps to direct the surgeon to choose the appropriate management of biliary pain in absence of biliary stone.

A recent review and meta-analysis of 10 publications (416 patients) on the role of intrasphincteric (Oddi) injections of botulinum toxin in biliary pain demonstrated complete pain relief in 49% and partial pain relief in 64% of the patients [99]. In most patients, the pain relief was temporary and needed to be followed by endoscopic sphincterectomy. The authors concluded that botulinum toxin injection could be a potential option in the overall management strategy of patients with Type III sphincter of Oddi dysfunction,

Conclusion

The area of postsurgical pain and its management is a challenging issue for clinicians and surgeons. Preventive use of BoNT therapy is a novel approach which, if proven efficacious in additional studies, could lead to postsurgical pain relief in a large number of patients. Refinement of the injection technique and determination of the optimum dosage may help achieve better results and optimize botulinum toxin effect in this important area of pain medicine.

References

1. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology. 2013;118:934–44.
2. Bloom JR, Stewart SL, Oakley-Girvan I, et al. Quality of life of younger breast cancer survivors: persistence of problems and sense of well-being. Psychooncology. 2012;21:655–65. https://doi.org/10.1002/pon.1965.
3. Høyer M, Johansson B, Nordin K, et al. Health-related quality of life among women with breast cancer: a population-based study. Acta Oncol. 2011;50:1015–26.
4. Schop SSJ, Hommes JE, Krastev TK, Derks D, Larsen M, Rakhorst H, Schmidbauer U, Smit JM, Tan T, Wehrens K, de Wit T, van der Hulst RRWJ, Piatkowski de Grzymala AA. BREAST trial study protocol: evaluation of a non-invasive technique for breast reconstruction in a multicentre, randomised controlled trial. BMJ Open. 2021;11(9):e051413. https://doi.org/10.1136/bmjopen-2021-051413. PMID: 34531218; PMCID: PMC8449986
5. Eltahir Y, Werners LLCH, Dreise MM, et al. Quality-of-life outcomes between mastectomy alone and breast reconstruction: comparison of patient-reported BREAST-Q and other health-related quality-of-life measures. Plast Reconstr Surg. 2013;132:201e–9. https://doi.org/10.1097/PRS.0b013e31829586a7.
6. Zhong T, McCarthy C, Min S, et al. Patient satisfaction and health-related quality of life after autologous tissue breast reconstruction. Cancer. 2012;118:1701–9.
7. Gabriel A, Maxwell P. Use of botulinum toxin in post-mastectomy breast reconstruction. In: Jabbari B, editor. Botulinum toxin treatment in surgery dentistry and veterinary medicine. Cham: Springer Nature; 2020. p. 187–94.
8. Senior M. Botox and the management of pectoral spasm after subpectoral implant insertion. Plast Reconstr Surg. 2000;106:224.
9. Wong L. Pectoralis major myospasm resulting from a subpectoral implant. Plast Reconstr Surg. 2000;105:1571.
10. Disa JJ, Ad-El DD, Cohen SM, Cordeiro PG, Hidalgo DA. The premature removal of tissue expanders in breast reconstruction. Plast Reconstr Surg. 1999;104(6):1662–5. https://doi.org/10.1097/00006534-199911000-00008. PMID: 10541166
11. Gur E, Hanna W, Andrighetti L, Semple JL. Light and electron microscopic evaluation of the pectoralis major muscle following tissue expansion for breast reconstruction. Plast Reconstr Surg. 1998;102:1046–51.
12. Mast BA. Painful pectoralis major myospasm as a result of sternal wound reconstruction: complete resolution with bilateral pectoral neurectomies. Plast Reconstr Surg. 1999;104:798–800.
13. Hoffman GW, Elliot LF. The anatomy of the pectoral nerves and its significance to the general and plastic surgeon. Ann Surg. 1987;205:504–7.

14. Marcusa DP, Mann RA, Cron DC, Fillinger BR, Rzepecki AK, Kozlow JH, Momoh A, Englesbe M, Brummett C, Waljee JF. Prescription opioid use among opioid-naive women undergoing immediate breast reconstruction. Plast Reconstr Surg. 2017;140(6):1081–90. https://doi.org/10.1097/PRS.0000000000003832. PMID: 29176408
15. Nahabedian MY. Current approaches to Prepectoral breast reconstruction. Plast Reconstr Surg. 2018;142(4):871–80. https://doi.org/10.1097/PRS.0000000000004802. PMID: 30252807
16. Christo PJ, Mazloomdoost D. Cancer pain and analgesia. Ann NY Acad Sci. 2008;1138:278–98. https://doi.org/10.1196/annals.1414.033. PMID: 18837907
17. Darrach H, Kraenzlin FS, Khavanin N, He W, Lee E, Sacks JM. Pectoral placement of tissue expanders affects inpatient opioid use. Breast J. 2021;27(2):126–33. https://doi.org/10.1111/tbj.14149. Epub 2021 Jan 12. PMID: 33438303
18. Abdelsattar JM, Degnim AC, Hieken TJ, Saint-Cyr M, Boughey JC. Local infiltration of liposomal bupivacaine for pain control in patients undergoing mastectomy with immediate tissue expander reconstruction. Ann Surg Oncol. 2015;22(10):3402–3. https://doi.org/10.1245/s10434-015-4670-5. Epub 2015 Jul 23. PMID: 26202558
19. Pacik PT, Nelson CE, Werner C. Pain control in augmentation mammaplasty using indwelling catheters in 687 consecutive patients: data analysis. Aesthet Surg J. 2008;28(6):631–41. https://doi.org/10.1016/j.asj.2008.09.001. PMID: 19083591
20. Scheflan M, Allweis TM. What can breast and plastic surgeons do to help fight the opioid crisis: the interpectoral block for pain control following aesthetic and reconstructive breast surgery. Aesthet Surg J Open Forum. 2020;2(1):ojaa009. https://doi.org/10.1093/asjof/ojaa009. PMID: 33791629; PMCID: PMC7780501
21. Rossetto O, Pirazzini M, Fabris F, Montecucco C. Botulinum neurotoxins: mechanism of action. Handb Exp Pharmacol. 2021;263:35–47. https://doi.org/10.1007/164_2020_355. PMID: 32277300
22. Bach-Rojecky L, Relja M, Lacković Z. Botulinum toxin type A in experimental neuropathic pain. J Neural Transm (Vienna). 2005;112(2):215–9. https://doi.org/10.1007/s00702-004-0265-1. PMID: 15657640
23. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;358:137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 Jul 1. PMID: 28673722
24. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155(4):674–84. https://doi.org/10.1016/j.pain.2013.12.009. Epub 2013 Dec 11. PMID: 24333775; PMCID: PMC3960322.
25. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107(1–2):125–33. https://doi.org/10.1016/j.pain.2003.10.008. PMID: 14715398
26. Mika J, Rojewska E, Makuch W, Korostynski M, Luvisetto S, Marinelli S, Pavone F, Przewlocka B. The effect of botulinum neurotoxin A on sciatic nerve injury-induced neuroimmunological changes in rat dorsal root ganglia and spinal cord. Neuroscience. 2011;175:358–66. https://doi.org/10.1016/j.neuroscience.2010.11.040. Epub 2010 Nov 25. PMID: 21111791
27. Bossowska A, Lepiarczyk E, Mazur U, Janikiewicz P, Markiewicz W. Botulinum toxin type A induces changes in the chemical coding of substance P-immunoreactive dorsal root ganglia sensory neurons supplying the porcine urinary bladder. Toxins (Basel). 2015;7(11):4797–816. https://doi.org/10.3390/toxins7114797. PMID: 26580655; PMCID: PMC4663534
28. Wang W, Kong M, Dou Y, Xue S, Liu Y, Zhang Y, Chen W, Li Y, Dai X, Meng J, Wang J. Selective expression of a SNARE-cleaving protease in peripheral sensory neurons attenuates pain-related gene transcription and neuropeptide release. Int J Mol Sci. 2021;22(16):8826. https://doi.org/10.3390/ijms22168826. PMID: 34445536; PMCID: PMC8396265
29. Shin MC, Wakita M, Xie DJ, Yamaga T, Iwata S, Torii Y, Harakawa T, Ginnaga A, Kozaki S, Akaike N. Inhibition of membrane Na+ channels by A type botulinum toxin at femtomolar

concentrations in central and peripheral neurons. J Pharmacol Sci. 2012;118(1):33–42. https://doi.org/10.1254/jphs.11060fp. Epub 2011 Dec 10. PMID: 22156364
30. Hong B, Yao L, Ni L, Wang L, Hu X. Antinociceptive effect of botulinum toxin A involves alterations in AMPA receptor expression and glutamate release in spinal dorsal horn neurons. Neuroscience. 2017;357:197–207. https://doi.org/10.1016/j.neuroscience.2017.06.004. Epub 2017 Jun 10. PMID: 28606856
31. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin Type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459. PMID: 31387301; PMCID: PMC6723487
32. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012;61(2):236–9. https://doi.org/10.1016/j.neuint.2012.05.001. Epub 2012 May 8. PMID: 22580329
33. Lacković Z. Botulinum toxin and pain. Handb Exp Pharmacol. 2021;263:251–64. https://doi.org/10.1007/164_2019_348. PMID: 32016565
34. Drinovac Vlah V, Filipović B, Bach-Rojecky L, Lacković Z. Role of central versus peripheral opioid system in antinociceptive and anti-inflammatory effect of botulinum toxin type A in trigeminal region. Eur J Pain. 2018;22(3):583–91. https://doi.org/10.1002/ejp.1146. Epub 2017 Nov 13. PMID: 29134730
35. 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(9):1358–73. https://doi.org/10.1111/j.1526-4610.2011.01990.x. Epub 2011 Aug 29. PMID: 21883197
36. Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC, Aurora SK, Sirimanne M, DeGryse RE, Turkel CC, Dodick DW. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013;331(1–2):48–56. https://doi.org/10.1016/j.jns.2013.05.003. Epub 2013 Jun 19. PMID: 23790235
37. 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(17):1473–8. https://doi.org/10.1212/01.wnl.0000345968.05959.cf. Epub 2009 Feb 25. PMID: 19246421
38. 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(12):1827–33. https://doi.org/10.1111/j.1526-4637.2010.01003.x. PMID: 21134121
39. Childers MK, Wilson DJ, Gnatz SM, Conway RR, Sherman AK. Botulinum toxin type A use in piriformis muscle syndrome: a pilot study. Am J Phys Med Rehabil. 2002;81(10):751–9. https://doi.org/10.1097/00002060-200210000-00006. PMID: 12362115
40. Wu CJ, Lian YJ, Zheng YK, Zhang HF, Chen Y, Xie NC, Wang LJ. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32(6):443–50. https://doi.org/10.1177/0333102412441721. Epub 2012 Apr 5. PMID: 22492424
41. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol. 2016;79(4):569–78. https://doi.org/10.1002/ana.24605. Epub 2016 Feb 16. PMID: 26814620; PMCID: PMC4825405.
42. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol. 2008;64(3):274–83. https://doi.org/10.1002/ana.21427. Erratum in: Ann Neurol. 2009;65(3):359. PMID: 18546285
43. Akalin Ç, Yavuzarslan AB, Akyol C. Efficacy and safety of Endoanal ultrasound-guided botulinum toxin in chronic anal fissure. Am Surg. 2021;31348211034750 https://doi.org/10.1177/00031348211034750. Epub ahead of print. PMID: 34313489
44. 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(4):915–23. https://doi.org/10.1097/01.AOG.0000237100.29870.cc. PMID: 17012454

45. Winocour S, Murad MH, Bidgoli-Moghaddam M, Jacobson SR, Bite U, Saint-Cyr M, Tran NV, Lemaine V. A systematic review of the use of Botulinum toxin type A with subpectoral breast implants. J Plast Reconstr Aesthet Surg. 2014;67:34–41.
46. Layeeque R, Hochberg J, Siegel E, Kunkel K, Kepple J, Henry-Tillman RS, Dunlap M, Seibert J, Klimberg VS. Botulinum toxin infiltration for pain control after mastectomy and expander reconstruction. Ann Surg. 2004;240:608–13.
47. Lo KK, Aycock JK. A blinded randomized controlled trial to evaluate the use of botulinum toxin for pain control in breast reconstruction with tissue expanders. Ann Plast Surg. 2015;74(3):281–3. https://doi.org/10.1097/SAP.0b013e31829be8d8. PMID: 23903088
48. Gabriel A, Champaneria MC, Maxwell GP. The efficacy of botulinum toxin A in post-mastectomy breast reconstruction: a pilot study. Aesthet Surg J. 2015;35(4):402–9. https://doi.org/10.1093/asj/sjv040. Epub 2015 Mar 29. PMID: 25825421
49. Lemaine V, Lohse CM, Mandrekar JN, Ramaker SA, Convery PA, Nguyen MD, Tran NV. Botulinum Toxin A in tissue expander breast reconstruction: a double-blinded randomized controlled trial. Plast Reconstr Surg Glob Open. 2020;8(8):e3030. https://doi.org/10.1097/GOX.0000000000003030. PMID: 32983785; PMCID: PMC7489665
50. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology. 2008;71(20):1639–43. https://doi.org/10.1212/01.wnl.0000336535.27773.c0. PMID: 19001255
51. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008;71(20):1634–8. https://doi.org/10.1212/01.wnl.0000336533.19610.1b. PMID: 19001254
52. Altomare DF, Giannini I. Pharmacological treatment of hemorrhoids: a narrative review. Expert Opin Pharmacother. 2013;14:2343–9.
53. Loder PB, Kamm MA, Nicholls RJ, Phillips RK. Hemorrhoids: pathology, pathophysiology and etiology. Br J Surg. 1994;81:946–54.
54. Johanson JF, Sonnenberg A. Temporal changes in the occurrence of hemorrhoids in the United States and England. Dis Colon Rectum. 1991;34:585–91.
55. Tiret L, Rotman N, Hatton F, Fagniez PL. Digestive surgery in France. A national epidermiologic survey (1978-1982). Gastroenterol Clin Biol. 1988;12:354–60.
56. Medina-Gallardo A, Curbelo-Peña Y, De Castro X, Roura-Poch P, Roca-Closa J, De Caralt-Mestres E. Is the severe pain after Milligan-Morgan hemorrhoidectomy still currently remaining a major postoperative problem despite being one of the oldest surgical techniques described? A case series of 117 consecutive patients. Int J Surg Case Rep. 2017;30:73–5. https://doi.org/10.1016/j.ijscr.2016.11.018. Epub 2016 Nov 15. PMID: 27960130; PMCID: PMC5153430.
57. Elton C, Sen P, Montgomery AC. Initial study to assess the effects of topical glyceryl trinitrate for pain after haemorrhoidectomy. Int J Surg Investig. 2001;2:353–7.
58. Hwang DY, Yoon SG, Kim HS, Lee JK, Kim KY. Effect of 0.2 percent glyceryl trinitrate ointment on wound healing after a hemorrhoidectomy: results of a randomized, prospective, doubleblind, placebo-controlled trial. Dis Colon Rectum. 2003;46:950–4.
59. Tan KY, Sng KK, Tay KH, Lai JH, Eu KW. Randomized clinical trial of 0.2 per cent glyceryl trinitrate ointment for wound healing and pain reduction after open diathermy haemorrhoidectomy. Br J Surg. 2006;93:1464–8.
60. Khan KI, Waqas A, Akmal M, Mahmood S, Iqbal A. Efficacy of combination of 0.2% GTN and lignocaine ointments in wound healing and pain relief after Milligan Morgan hemorrhoidectomy – a comparison with lignocaine and 0.2% GTN ointments separately. Int J Surg. 2014;12:329–33.
61. Amoli HA, Notash AY, Shahandashti FJ, Kenari AY, Ashraf H. A randomized, prospective, double-blind, placebo-controlled trial of the effect of topical diltiazem on post-hemorrhoidectomy pain. Color Dis. 2011;13:328–32.
62. Perrotti P, Dominici P, Grossi E, Cerutti R, Antropoli C. Topical nifedipine with lidocaine ointment versus active control for pain after hemorrhoidectomy: results of a multicentre, prospective, randomized double-blind study. Can J Surg. 2010;53:17–24.

63. Re AD, Toh JWT, Iredell J, Ctercteko G. Metronidazole in the management of post-open haemorrhoidectomy pain: systematic review. Ann Coloproctol. 2020;36(1):5–11. https://doi.org/10.3393/ac.2020.01.08. Epub 2020 Feb 29. PMID: 32146782; PMCID: PMC7069672.
64. Carapeti EA, Kamm MA, McDonald PJ, Phillips RK. Double-blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy. Lancet. 1998;351:169–72.
65. Miyachi Y, Imamura S, Niwa Y. Anti-oxidant action of metronidazole: a possible mechanism of action in rosacea. Br J Dermatol. 1986;114:231–4.
66. Ho KS, Eu KW, Heah SM, Seow-Choen F, Chan YW. Randomized clinical trial of haemorrhoidectomy under a mixture of local anaesthesia versus general anaesthesia. Br J Surg. 2000;87:410–3.
67. Luck AJ, Hewett PJ. Ischiorectal fossa block decreases posthemorrhoidectomy pain: randomized, prospective, double-blind clinical trial. Dis Colon Rectum. 2000;43:142–5.
68. Kilbride M, Morse M, Senagore A. Transdermal fentanyl improves management of postoperative hemorrhoidectomy pain. Dis Colon Rectum. 1994;37:1070–2.
69. Andrews BT, Layer GT, Jackson BT, Nicholls RJ. Randomized trial comparing diathermy hemorrhoidectomy with scissor dissection Milligan-Morgan operation. Dis Colon Rectum. 1993;36:580–3.
70. Siddiqui MR, Abraham-Igwe C, Shangumanandan A, Grassi V, Swift I, Abulafi AM. A literature review on the role of chemical sphincterotomy after hemorrhoidectomy. Milligan-Morgan. Int J Colorectal Dis. 2011;26:685–92.
71. Lu PW, Fields AC, Andriotti T, Welten VM, Rojas-Alexandre M, Koehlmoos TP, Schoenfeld AJ, Melnitchouk N. Opioid prescriptions after hemorrhoidectomy. Dis Colon Rectum. 2020;63(8):1118–26. https://doi.org/10.1097/DCR.0000000000001570. PMID: 32015286
72. Balciscueta Z, Balciscueta I, Uribe N. Post-hemorrhoidectomy pain: can surgeons reduce it? A systematic review and network meta-analysis of randomized trials. Int J Color Dis. 2021; https://doi.org/10.1007/s00384-021-04013-6. Epub ahead of print. PMID: 34417639
73. Davies J, Duffy D, Boyt N, Aghahoseini A, Alexander D, Leveson S. Botulinum toxin (botox) reduces pain after hemorrhoidectomy: results of a double-blind, randomized study. Dis Colon Rectum. 2003;46:1097–102.
74. Patti R, Almasio PL, Muggeo VM, Buscemi S, Arcara M, Matranga S, Di Vita G. Improvement of wound healing after hemorrhoidectomy: a double-blind, randomized study of botulinum toxin injection. Dis Colon Rectum. 2005;48:2173–9.
75. Patti R, Arcara M, Bonventre S, Sammartano S, Sparacello M, Vitello G, Di Vita G. Randomized clinical trial of botulinum toxin injection for pain relief in patients with thrombosed external haemorrhoids. Br J Surg. 2008;95:1339–43.
76. Singh B, Box B, Lindsey I, George B, Mortensen N, Cunningham C. Botulinum toxin reduces anal spasm but has no effect on pain after hemorrhoidectomy. Color Dis. 2009;11:203–7.
77. Sirikurnpiboon S, Jivapaisarnpong P. Botulinum toxin injection for analgesic effect after hemorrhoidectomy: a randomized control trial. J Anus Rectum Colon. 2020;4(4):186–92. https://doi.org/10.23922/jarc.2020-027. PMID: 33134600; PMCID: PMC7595677
78. Patti R, Almasio PL, Arcara M, Sammartano S, Romano P, Fede C, Di Vita G. Botulinum toxin vs. topical glyceryl trinitrate ointment for pain control in patients undergoing hemorrhoidectomy: a randomized trial. Dis Colon Rectum. 2006;49:1741–8.
79. Eriksen JR, Poornoroozy P, Jørgensen LN, Jacobsen B, Friis-Andersen HU, Rosenberg J. Pain, quality of life and recovery after laparoscopic ventral hernia repair. Hernia. 2009;13:13–21.
80. Zielinski MD, Goussous N, Schiller HJ, Jenkins D. Chemical components separation with botulinum toxin A: a novel technique to improve primary fascial closure rates of the open abdomen. Hernia. 2013;17(1):101–7. https://doi.org/10.1007/s10029-012-0995-1. Epub 2012 Sep 22. PMID: 23001400
81. Ibarra-Hurtado TR, Nuño-Guzmán CM, Echeagaray-Herrera JE, Robles-Vélez E, de Jesús González-Jaime J. Use of botulinum toxin type a before abdominal wall hernia reconstruction.

World J Surg. 2009;33(12):2553–6. https://doi.org/10.1007/s00268-009-0203-3. Epub 2009 Sep 22. PMID: 19771472
82. Ibarra-Hurtado TR, Nuño-Guzmán CM, Miranda-Díaz AG, Troyo-Sanromán R, Navarro-Ibarra R, Bravo-Cuéllar L. Effect of botulinum toxin type A in lateral abdominal wall muscles thickness and length of patients with midline incisional hernia secondary to open abdomen management. Hernia. 2014;18(5):647–52. https://doi.org/10.1007/s10029-014-1280-2. Epub 2014 Jul 18. PMID: 25033942
83. Elstner KE, Jacombs AS, Read JW, Rodriguez O, Edye M, Cosman PH, Dardano AN, Zea A, Boesel T, Mikami DJ, Craft C, Ibrahim N. Laparoscopic repair of complex ventral hernia facilitated by pre-operative chemical component relaxation using Botulinum Toxin A. Hernia. 2016;20(2):209–19. https://doi.org/10.1007/s10029-016-1478-6. Epub 2016 Mar 7. PMID: 26951247
84. Elstner KE, Read JW, Rodriguez-Acevedo O, Cosman PH, Dardano AN, Jacombs AS, Edye M, Zea A, Boesel T, Mikami DJ, Ibrahim N. Preoperative chemical component relaxation using Botulinum toxin A: enabling laparoscopic repair of complex ventral hernia. Surg Endosc. 2017;31(2):761–8. https://doi.org/10.1007/s00464-016-5030-7. Epub 2016 Jun 28. PMID: 27351658
85. Soltanizadeh S, Helgstrand F, Jorgensen LN. Botulinum toxin a as an adjunct to abdominal wall reconstruction for incisional hernia. Plast Reconstr Surg Glob Open. 2017;5(6):e1358. https://doi.org/10.1097/GOX.0000000000001358. PMID: 28740773; PMCID: PMC5505834
86. Weissler JM, Lanni MA, Tecce MG, Carney MJ, Shubinets V, Fischer JP. Chemical component separation: a systematic review and meta-analysis of botulinum toxin for management of ventral hernia. J Plast Surg Hand Surg. 2017;51(5):366–74. https://doi.org/10.1080/2000656X.2017.1285783. Epub 2017 Feb 20. PMID: 28277071
87. Rodriguez-Acevedo O, Elstner KE, Jacombs ASW, Read JW, Martins RT, Arduini F, Wehrhahm M, Craft C, Cosman PH, Dardano AN, Ibrahim N. Preoperative Botulinum toxin A enabling defect closure and laparoscopic repair of complex ventral hernia. Surg Endosc. 2018;32(2):831–9. https://doi.org/10.1007/s00464-017-5750-3. Epub 2017 Jul 21. PMID: 28733748
88. Tamboli M, Kitamura R, Ma W, Kumar G, Harrison TK, Wang RR, Mariano ER, Leng JC. Preoperative ultrasound-guided botulinum toxin a injection facilitates closure of a complex abdominal Wall hernia: a case report. A A Pract. 2019;13(5):193–6. https://doi.org/10.1213/XAA.0000000000001033. PMID: 31180908
89. Zendejas B, Khasawneh MA, Srvantstyan B, Jenkins DH, Schiller HJ, Zielinski MD. Outcomes of chemical component paralysis using botulinum toxin for incisional hernia repairs. World J Surg. 2013;37:2830–7.
90. Blaha L, Chouliaras K, White A, McNatt S, Westcott C. Intraoperative botulinum toxin chemodenervation and analgesia in abdominal wall reconstruction. Surg Innov. 2020;1553350620975253 https://doi.org/10.1177/1553350620975253. Epub ahead of print. PMID: 33234030
91. Mallet C, Ilharreborde B, Presedo A, Khairouni A, Mazda K, Penneçot GF. One-stage hip reconstruction in children with cerebral palsy: long-term results at skeletal maturity. J Child Orthop. 2014. [Epub ahead of print]
92. Barwood S, Baillieu C, Boyd R, Brereton K, Low J, Nattrass G, Graham HK. Analgesic effects of botulinum toxin a: a randomized, placebo-controlled clinical. Dev Med Child Neurol. 2000;42:116–21.
93. Sherman S, Lehman GA. Sphincter of Oddi dysfunction: diagnosis and treatment. JOP. 2001;2:382–400.
94. Murray WR. Reducing the incidence and severity of post ERCP pancreatitis. Scand J Surg. 2005;94:112–6.
95. Geenen JE, Hogan WJ, Dodds WJ, Toouli J, Venu RP. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter of Oddi dysfunction. N Engl J Med. 1989;320:82–7.

96. Wehrmann T, Seifert H, Seipp M, Lembcke B, Caspary WF. Endoscopic injection of botulinum toxin for biliary sphincter of Oddi dysfunction. Endoscopy. 1998;30(8):702–7.
97. Murray W, Kong S. Botulinum toxin may predict the outcome of endoscopic sphincterotomy in episodic functional post-cholecystectomy biliary pain. Scand J Gastroenterol. 2010;45:623–7.
98. Murray WR. Botulinum toxin-induced relaxation of the sphincter of Oddi may select patients with acalculous biliary pain who will benefit from cholecystectomy. Surg Endosc. 2011;25(3):813–6. https://doi.org/10.1007/s00464-010-1260-2. Epub 2010 Jul 28. PMID: 20665051
99. Menon S, Kurien R, Mathew R. The role of intrasphincteric botulinum toxin injection in the management of functional biliary pain: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2020;32(8):984–9. https://doi.org/10.1097/MEG.0000000000001773. PMID: 32453006

Chapter 15
Botulinum Toxins (BoNTs) for Treatment of Pain in Orthopedic Disorders

Introduction

Osteoarthritis is the most common cause of chronic joint pain and the most common cause of disability in the United States [1]. In the United States, currently, 27 million people are affected by chronic osteoarthritis, a number that is suspected to increase to 67 million by the year 2030 [2, 3].

In vitro and in vivo animal studies have shown that botulinum neurotoxins reduce the action of pain transmitters via their action peripherally (nerve terminal and peripheral neurons) and centrally (via retrograde transfer and transcytosis) [4–17]. Furthermore, double-blind, placebo-controlled studies have proven or highly suggest their efficacy in several common human pain disorders such as chronic migraine, trigeminal neuralgia, post-herpetic and post- traumatic neuralgias, and neuropathic pain arising from peripheral or central trauma [18–28]. In general, BoNT therapy in pain disorders is considered safe when used in appropriate doses [29].

Over the past 20 years, several publications have pointed to the usefulness of botulinum neurotoxin (BoNT) therapy in orthopedic conditions associated with chronic pain. In this chapter, we will discuss four such disorders in which blinded, placebo-controlled studies as well as open-label investigations have reported the beneficial and analgesic effect of botulinum neurotoxins. The discussed orthopedic categories covered in this chapter consist of chronic lateral epicondylitis, refractory pain after total knee arthroplasty (TKA), chronic joint pain related to arthritis, and anterior knee pain with vastus lateralis imbalance.

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_15

Chronic Lateral Epicondylitis (CLE)

Lateral epicondylitis (LE) is a clinical condition characterized by pain in the elbow related to overuse of the joint. It is especially prevalent among tennis players (tennis elbow) and in individuals lifting heavy weights and using frequent elbow flexion and extension. Lateral epicondylitis is a common disorder with an incidence of 15.1/10,000 [30] and a prevalence of 4–7/1000 patients per year [31, 32]. In clinical practice, a substantial number of patients with acute LE recover within 12 months [33]. The small percentage that evolves into the chronic LE often resists responding to pharmacotherapy.

Currently, it is believed that degeneration of the extensor tendons is responsible for the clinical symptoms [34], but the role of inflammation is still considered despite the paucity of pathological evidence. Ultrasound studies of the affected joint have supported the concept of tendinopathy and tendon degeneration [35].

On examination, maximal tenderness is felt over the lateral epicondyle. Sometimes palpation of the entire tendon or the connecting muscle (extensor carpi ulnaris) may exhibit tightness. Pain can be produced by resisting wrist extension during elbow extension and forearm pronation. Resisting extension of the middle finger while the elbow is extended is usually painful due to increased stress upon the affected tendon.

Treatment of CLE includes avoiding exposure of the affected elbow to heavy load, bracing, physical therapy, pharmacotherapy, and surgery. Pharmacotherapy includes usage of analgesic medications such as cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs, GABAergic analgesics (gabapentin and pregabalin), and, in recalcitrant cases, opioid analgesics. Acupuncture, extracorporeal shock therapy, and autologous-rich plasma have been tried in clinical trials, but proof of their efficacy requires studies with a larger number of patients and higher quality [36–38]. In some patients, local injection of normal saline improves pain in CLE [39]. Local injection of steroid is often effective, but an efficacy beyond 8 weeks is not proven [40]. Surgery is reserved for recalcitrant pain in CLE. Currently, many surgeons prefer arthroscopic intervention to open surgery [41].

Botulinum Neurotoxin Studies in CLE

The effect of BoNT injections on symptoms of chronic lateral epicondylitis has been reported in five placebo-controlled, double-blind and three double-blind, comparative studies (Tables 15.1 and 5.2).

Table 15.1 Double-blind, placebo-controlled studies investigating the efficacy of BoNT injections in chronic lateral epicondylitis (CLE)

Authors and date	Class	# Pts	Study type	Toxin	Dose, units	PO	SO	Results
Wong et al. [42]	II	60	DB, PC	aboA	60	VAS assessed at 12 weeks post-injection	Handgrip	Significant VAS improvement ($P < 0.001$)
Hayton et al. [43]	III	40	DB, PC	aboA	50	VAS assessed at 12 weeks post-injection	Hand grip, SF12	No improvement
Placzek et al. [44]	II	130	DB, PC	aboA	60	VAS assessed at,2,6,12, and 16 weeks post-injection	PPS	VAS and PPS improved at all weeks (P values for both <0.05)
Spandar et al. [45]	II	48	DB, PC	aboA	60	VAS assessed at 4,8,16 weeks post-injection	MP, MGS	VAS and MP improved significantly at 4 and 8 weeks (P values = 0.01 and 0.04, respectively).
Creuzé et al. [46]	II	37	DB, PC	onaA	40	Percentage of patients who reported >50% reduction of pain at 12 weeks post-injection	Pain intensity (VAS); pain frequency, MGS, quality of life, side effects assessed at 30 and 90 days post-injection	At 3 months, 15 patients in toxin group and 7 in saline group reported >50% pain reduction ($P = 0.005$). All SOs also improved significantly in the toxin group ($P < 0.05$)

In Table 1, study class is defined according to definition of the Assessment Subcommittee of AAN [47, 48]. *DBPC*, double-blind, placebo-controlled, *DBPC* double-blind, placebo-controlled, *aboA* abobotulinumtoxinA, *onaA* onabotulinumtoxinA, *PO* primary outcome, *SO* secondary outcome, *PPS* patient and physician satisfaction scale (0–4), *MP* maximum pinch, *MGS* maximum grip strength, SF12, health-related quality of life questionnaire

Placebo-Controlled Studies

Wong et al. [42] evaluated the efficacy of abobotulinumtoxinA (aboA) in 60 subjects (49 women) with CLE in a double-blind, placebo-controlled study. The primary outcome was reduction of pain in VAS (0–100 mm) at weeks 4 and 12. Handgrip strength was defined as a secondary outcome. The toxin group received 60 units of aboA diluted in 1 cc of normal saline. The injections (saline or toxin) were administered "deeply into the subcutaneous tissue and muscle, 1 cm from the lateral epicondyle, and were aimed toward the tender spot."

Table 15.2 Studies comparing the effect of botulinum toxin and steroid in lateral epicondylitis

Authors and date	Class	# Pts	Study type	Toxin	Dose, units	PO	SO	Results
Line et al. [49]	II	16	DB, PC	onaA Triamcinolone	50; 40	VAS assessed at 4,8,12 weeks after injection	Grip strength; WHOQoL-Brief (quality of life)	VAS score diminished after both treatments, but at 4 weeks, triamcinolone group had lower VAS score (0.04). No difference after week 4
Gou et al. [50]	II	26	DB, PC	OonaA into LE OnaA into tender point Triamcinolone	20; 20; 40	VAS at 4 weeks after injection	PRTEE MGS Functional status	Triamcinolone was superior to onaA injection into muscle tender points at week 4 post-injection—VAS ($P = 0.006$), MGS ($P = 0.03$), PRTEE ($P = 0.02$)

OnaA onabotulinumtoxinA (Botox), *DBPC* double-blind, placebo-controlled, *PRTEE* Patient-Rated Tennis Elbow Evaluation, *MGS* maximum grip strength, *WHOQoL-Brief* World Health Organization Quality of Life-Brief Questionnaire, *LE* lateral epicondyle, *PO* primary outcome, *SO* secondary outcome

The mean VAS scores for the botulinum group at baseline and at 4 weeks were 65.5 mm and 25.3 mm, respectively. For the placebo group, the VAS scores were 66.2 mm and 50.5 mm at the same time points, denoting a significant pain relief in favor of the toxin ($P < 0.001$). At week 12, mean VAS scores were 23.5 mm for the botulinum group and 43.5 mm for the placebo group, again supporting an analgesic effect for aboA ($P = 0.006$). The grip strength decreased in both groups slightly, but the difference between the two groups was not statistically significant. At 4 weeks, four patients on aboA experienced transient paralysis of finger extension.

In another blinded and controlled study, Hayton et al. [43] compared the effect of abobotulinum toxin A (50 units) with saline in 40 patients with CLE who had failed to respond to steroid therapy. The injections were intramuscular and performed 5 cm distal to the maximum point of tenderness at the lateral epicondyle, in line with the middle of the wrist. Investigators assessed pain with visual analog scale, the quality of life with short form SF12 and handgrip with Jamar dynamometer

before injection and 3 months after injection. They found no difference between the toxin and the placebo with the aforementioned assessments at 3 months.

Placzek et al. [44] conducted a multicenter, double-blind, placebo-controlled RTC in 130 patients with CLE. The toxin group (70 patients) received 60 units of abobotulinumtoxinA diluted in 0.6 cc of saline (0.9%). The control group (62 patients) received the same volume of saline. The solution (toxin or saline) was injected 3–4 centimeters distal to the tender epicondyle and at two locations reflecting different depths after partial withdrawal of the needle following injection of ½ of the solution. The level of pain was assessed by VAS at baseline (before injection) and at 2, 6, 12, and 18 weeks. Patients' and physician's satisfaction was measured on a score of 0 (substantially worse) to 4 (substantially better) at the same time points. The strength of finger extension was also measured by a vigometer in all patients. Injection of aboA resulted in significant improvement of pain at all time points after injection (2, 6, 12, and 18 weeks) ($P < 0.05$) (Table 15.1).

Espandar et al. [45] conducted a randomized, placebo-controlled study of 48 patients with chronic refractory lateral epicondylitis. The patients in the toxin group (24 patients) received 60 units of abobotulinumtoxinA, and the control group (24 patients) received the same volume of normal saline. The site of injection was chosen based on prior studies on cadavers (Liu et al. 1997)—33% of the arm length below the lateral epicondyle. In most individuals, the posterior interosseous nerve innervates the extensor carpi ulnaris and extensor digitorum at this point. The primary outcome was intensity of pain at rest measured by VAS (0–100 mm) at 4, 8, and 16 weeks after injection. Secondary outcomes included intensity of pain during maximum pinch, maximum handgrip, and grip strength. The aboA group showed significant reduction of pain at rest compared to the placebo group at 4 weeks (14.1 mm), at 8 weeks (11.5 mm), and at 16 weeks (12.6 mm) ($P = 0.01$). Among the secondary outcomes, the intensity of pain during the maximum pinch was also decreased significantly in the aboA group compared to controls ($P = 0.004$). All patients in the toxin group developed some weakness of finer extensors which resolved by week 8. In one patient, weakness of third and fourth fingers which had developed at week 4 resolved by week 16 [46].

Creuze et al. [47] assessed the efficacy of onabotulinumtoxinA in a single-center, randomized, double-blind, placebo-controlled study of 57 patients. All patients had failed to respond to 6 months or more of other treatment(s) for their lateral epicondylitis. Twenty-nine patients received 40 units of onaA injection, and 28 patient received normal saline injections. Injections were guided by nerve stimulation into the extensor carpi ulnaris brevis muscle. The primary outcome of the study was the percentage of patients who demonstrated >50% reduction of pain in VAS score in 3 months. The secondary outcomes included pain frequency, maximum grip strength, side effects, and quality of life, assessed at 30 and 90 days, post-injection, as well as the number of patients per group requesting additional treatment by other therapeutic approaches at day 90.

In the toxin group, 15 patients (51%), and in the placebo group, 7 patients (25%), reported >50% reduction in initial pain intensity at day 90 ($P = 0.005$). Pain intensity (measured by VAS) and the effect on the quality of life were both significantly

improved in the BoNT-A treated group compared to the placebo at day 90 ($p < 0.05$). In the toxin group, 17.2% of patients developed transient weakness of extension of the third finger, with "no associated functional impairment."

Comparator Studies

Lin et al. [49] compared the effect of 50 units of onabotulinumtoxinA (onaA) with steroid injection (40 mg of triamcinolone acetonide) in a small double-blind study of 16 patients with acute and subacute lateral epicondylitis. OnabotulinumtoxinA (Botox) and triamcinolone were injected into the extensor carpi radialis brevis near the common origin of wrist and finger extensors of the affected elbow. The injected dose of onaA was 50 units, and that of triamcinolone was 40 mg. The level of pain, handgrip, and quality of life were assessed with VAS, dynamometer, and the World Health Organization's Quality of Life Brief (WHOQoL-Brief) questionnaire at baseline, 4, 8, and 12 weeks post-injection. VAS was the primary outcome measure. Both onabotulinumtoxinA and triamcinolone improved pain at 4, 8, and 12 weeks. At 4 weeks, the analgesic effect of triamcinolone was greater than onaA ($P = 0.02$). In the toxin group, the only side effect was mild weakness of wrist and middle finger extension that did not interfere with daily activities and cleared over 12 weeks.

Guo et al. [50] compared the effect of two injection sites of onabotulinumtoxinA with steroid (triamcinolone) in lateral epicondylitis. Patients were randomly assigned to three groups. One group (eight patients) received onaA injection into the lateral epicondyle (20 units). The second group (seven patients) received the same dose of the toxin into the most tender site of the extensor muscle. The third group (11 patients) was injected with 40 units of triamcinolone into the lateral epicondyle. The injector and rater were both blinded to the order and type of injection. The primary outcome was a change in the level of assessed pain by visual analog scale (VAS). Secondary outcomes included Patient-Rated Tennis Elbow Evaluation (PRTEE), dynamometer, maximum grip strength (MGS), and functional status. Patients were rated at baseline and at 4,8,12, and 16 weeks after injections.

There was no difference in regard to primary or secondary outcomes between triamcinolone and toxin group when injections performed into the lateral epicondyle region. Triamcinolone was, however, superior to the onaA injected into the muscle's tender points at week 4 following injection—VAS ($P = 0.006$), MHG ($P = 0.03$), PTEE ($P = 0.02$). However, there was no difference between the two groups beyond week 4.

Keizer et al. [51], in a randomized open-label study, compared the effect of BoNT-A injection with surgery (Hohmann extensor release) in 40 patients with chronic lateral epicondylitis (tennis elbow). Twenty patients were injected with BoNT-A, and 20 patients had surgery. Patients were evaluated at 3, 6, 12, and 24 months after toxin injections or surgery. At 12 months after treatment, 13 (65%) patients in the toxin group and 15 (75%) patients in the operated group demonstrated good to excellent results. At 24 months, 15 patients in the botulinum toxin

group (75%) and 17 patients (85%) in the operated group had good to excellent results. Since the difference between the two approaches was not statistically significant and botulinum toxin injection was less invasive, the authors recommended contemplating BoNT therapy before surgical intervention.

In a randomized, open-label clinical trial, Lim et al. [52] compared the effect of two different doses of Korean botulinumtoxinA (Meditox) in chronic lateral epicondylitis. Sixty patient participated in the study; half received 10 units and half 50 units of the toxin into extensor carpi radialis. They found both doses to be effective in relieving the symptoms, but the higher dose produced better results. The main side effect was the weakness of third finger extension.

Comment

Several open-label studies strongly suggest that marketed botulinumtoxinAs (abo, ona, and inco) are effective in reducing the pain of lateral epicondylitis [52–55]. The newer studies have benefited from the utilization of ultrasound to more precisely determine the optimal sites in the muscle for injection [52]. Among the randomized double-blind, placebo-controlled studies, four of five have shown significant reduction of pain after botulinum toxin injection into the wrist extensor (usually brevis) compared to the placebo injection [42, 44–46]. The study of Hyton et al. [43] did not show a difference between toxin (onA) and placebo injection in regard to pain relief in CLE, however. The reason could be partly due to the small number of patients in this study or the time of evaluation of the primary outcome since in many patients the effect of toxin starts to wane or is waned already at 3 months. Furthermore, almost an identical change was reported for toxin and placebo injections from baseline values after injections. This suggests the presence of a placebo effect that would make any conclusion drawn on the efficacy debatable. Considering the other four studies with positive results and using the efficacy criteria defined by the American Academy of Neurology [47, 48], the level of efficacy for botulinum toxin treatment of pain in chronic lateral epicondylitis would be B (probably effective) based on two or more class II published studies (Table 15.1).

The toxin versus steroid comparator studies (Table 15.2) claim superiority of triamcinolone injection over botulinum toxin in relieving the pain of lateral epicondylitis at 4 weeks post-injection. There are also some issues with these studies that require cautious interpretation of the data. For instance, in the study of Lin et al. [49], the number of subjects was too small (16). Furthermore, the baseline data showed a low pain level (mean 44 mm) for the toxin group and a higher level (mean 57.5 mm) for the triamcinolone group which might have influenced the results. Although the recent reviews of the efficacy of botulinum toxin in lateral epicondylitis have acknowledged the utility of toxin therapy in CLE, they strongly recommend conducting blinded studies with larger number of patients (preferably multicenter), in order to better define the role of botulinum toxin therapy in chronic lateral epicondylitis [56–58].

Weakness of the wrist and finger extensors that develops in a sizeable number of patients following BoNT injections into extensor carpi radialis remains a challenging issue for the toxin therapist in CLE. Song et al. [56], in a review of the literature, identified seven studies utilizing six different methods of injections. The largest reduction in pain was seen with injection at 1/3 of the length of the forearm from the lateral epicondyle. Gruner et al. [59] suggest that best results can be achieved by injecting at three sites, two separate sites into extensor carpi radialis and one site into the extensor tendon next to the lateral epicondyle. The best technique that causes the least weakness of finger and wrist muscles is yet to be identified when using BoNT injection for pain relief in CLE.

Intra-articular Use of Botulinum Neurotoxins for Treatment of Arthritic Pain

Introduction

Osteoarthritis is a huge health problem. A Global Burden of Disease Study reports that the incidence of osteoarthritis increased 102% in 2017 compared to 1990 [60]. In 2013, Cheng et al. [61] reviewed the literature on the efficacy of intra-articular (IA) injection of different agents for management of arthritic knee pain. Steroids and hyaluronate both showed efficacy; the latter provided possibly a longer duration of pain relief. Triamcinolone hexacetonide induced better results than triamcinolone acetonide and was recommended for this indication. Tropisetron and tanezumab were also found effective and were assigned a 2B+ efficacy level.

More recently several other treatment approaches have been introduced and are being investigated including application of autologous plasma-rich protein, combination of hyaluronic acid and clonidine (200 mg and 20 mg, respectively), intra-articular injection of intrapatellar stromal fat cell products, and specific peptides (for instance BPC-157) [62–65]. The application of these novel approaches requires further studies.

Botulinum Toxin Treatment

In this section, notable open-label clinical trials and double-blind, placebo-controlled studies investigating the efficacy of BoNTs in local osteoarthritis are described.

In 2006, Mahowald et al. [66] presented their one-year clinical experience with onaA injection for the treatment of arthritis and arthritic pain in 11 patients (nine shoulders, three knees, and three ankles). All studied patients had a history of failed prior treatments including intra-articular administration of steroids and/or visco-supplement agents. Patients were injected with onabotulinumtoxinA (onaA, Botox) into shoulder (50–100 units) as well as into the knee and ankle joints (25–50 units). The change in pain was calculated as raw change or percentage change. Upper

extremity function was assessed by degrees of active flexion and active abduction. Lower extremity function was measured by the "time to do sit to stand" for ten times. Patients were followed for 1 year with several assessments. Following intra-articular injection of onaA, the mean maximum reduction of joint pain (knee and ankle) was 55% ($p = 0.02$). The observed pain reduction was even greater in the shoulder joint reaching 72% ($p < 0.001$). Furthermore, significant improvements ($P < 0.05$) in lower extremity function (36%) and shoulder function (67% in flexion, 42% in abduction) were noted at follow-up assessments at 4 and10 weeks post toxin injection.

In 2011, Castiglione et al. [67] published the result of a prospective, open-label study on five patients who had post-hemiplegic shoulder pain (Fig. 15.1). They injected OnaA (100 units), aboA (500 units), and incoA (100 units) into the gleno-humeral painful joints in two, one, and two patients, respectively. The level of pain at rest and during passive arm abduction was assessed by VAS at 2 and 8 weeks post-injection. All subjects at both time points reported significant improvement of shoulder pain at rest and at arm abduction ($P = 0.001$ and $P < 0.001$, respectively). No difference in the level of pain relief was observed at 2 and 8 weeks.

McAlindon et al. [68] conducted a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-designed study on 158 patients with knee osteoarthritis. The patients' level of nociceptive pain was assessed through a painDETECT questionnaire (PD-Q). All intra-articular injections (toxin or saline) were performed under ultrasound guidance after aspiration of synovial fluid effusion (if present). The patients were stratified into three groups: onabotulinumtoxinA (200 units), onabotulinumtoxinA (400 units), and saline group. The duration of follow-up was 24 weeks. At 8 weeks post-injection, all three groups demonstrated decreased pain as measured by PD-Q. The level of reduction was 1.6, 2.1, and 2.1 points for 400u, 200u, and saline groups, respectively. This level of reduction was maintained for all three groups over the entire length of the study. The findings for the three groups

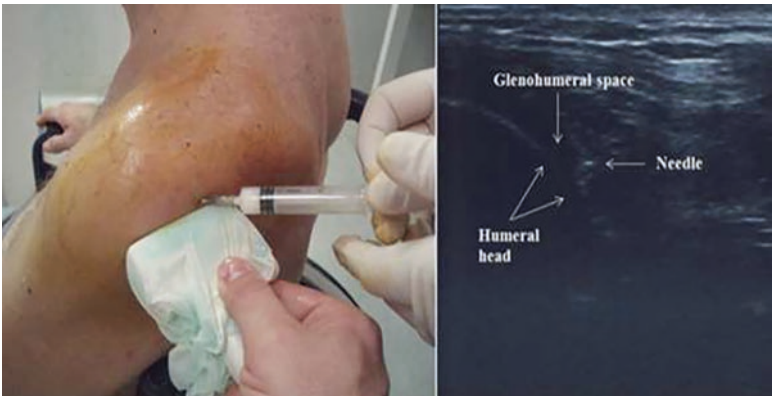

Fig. 15.1 Method of glenohumeral injection of BoNTs for hemiplegic refractory shoulder pain. From Gastiglione et al. (2011). Printed with permission from Archives of Physical Medicine and Rehabilitation

were similar for all secondary outcome measures including WOMAC physical function scores and the Patient Global Impression of Change (PGIC). The authors acknowledged a large placebo effect in their study. Also, the authors acknowledged that their pain scale, PD-Q, had never been validated for assessment of pain in knee arthritis.

In another double-blind, randomized, placebo-controlled, 12-week study, Arendt-Nielsen et al. (69) assessed the efficacy of BoNT therapy in painful osteoarthritis (OA) of the knee. A total of 121 patients with painful OA were randomly injected with either onabotulinumtoxinA (200 U, 2 ml) or the same volume of placebo (2 ml, 0.9% saline) and followed for 12 weeks. Injections were performed under ultrasound guidance. There were 61 patients in the toxin group and 60 subjects in the placebo group. Based on the painDETECT questionnaire, 68 patients had nociceptive type pain and 53 had non-nociceptive pain. Outcomes were evaluated through average daily pain score (ADP, 0–10 scale), Western Ontario and McMaster Universities, Osteoarthritic index (WOMAC) which includes a pain subset (0–20 scale), quantitative sensory testing, and Patient Global Impression of Change (PGIC). Patient's response was evaluated at baseline, at weeks 1, 4, 8, and 12 post-injection.

There was no statistically significant difference between the toxin and placebo group at baseline when all patients were compared. When the nociceptive group's response to toxin was compared with placebo in terms of change from baseline, the difference was statistically significant in several measures. These included changes in total WOMAC score and WOMAC pain subset score ($P = 0.029$ and $P = 0.021$, respectively), ADP score at 9 and 10 weeks ($P = 0.042$ and $P = 0.043$, respectively), PGIC at week 12 ($P = 0.03$), and reduction of rescue medication counts at weeks 9 and 10 ($P = 0.038$ and $P = 0.015$, respectively).

Elopatra et al. [70], in a double-blind, placebo-controlled study, assessed the analgesic effect of BoNT-A injections into thigh adductors in patients with chronic hip osteoarthritis. Patients were randomized into two groups; one group (31patients) was injected with 400 units of abobotulinumtoxinA (Dysport), and the other group (15 patients) was injected with normal saline. All injections were performed into the adductor thigh muscles. The authors defined two primary endpoints: (1) Harris Hip Score (HHS) and (2) Visual Analog Scale for pain (VAS). The difference between the two groups at week 4 post-injection was assessed. Secondary endpoints consisted of the change from baseline in Medical Research Council scale for muscle strength (MRC) and Short Form scale (SF-36) scores.

At week 4 post-injection, the HHS and VAS scores improved significantly in the toxin group compared to the placebo group ($P = 0.026$ and $P = 0.001$, respectively) (Fig. 15.2). Furthermore, the pairwise assessments showed significant improvements in HHS and VAS pain at each time point compared to baseline for the toxin group. There were no significant changes in MRC and SF-36 over time, but the SF-36 showed a positive trend improvement for quality of life in the toxin group. Authors reported no adverse events in either of the treatment groups.

Najafi et al. (71), in an open-label, prospective study, investigated the effectiveness of intra-articular injection of abobotulinumtoxinA (Dysport) in 30 patients (24

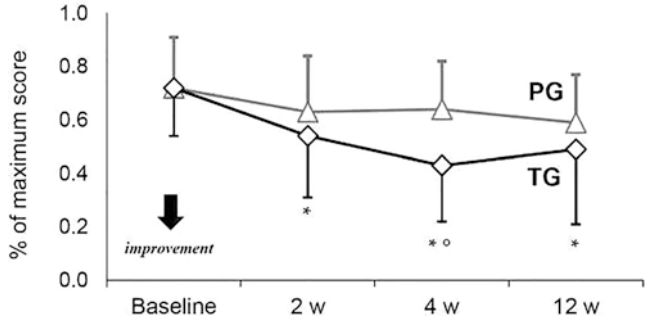

Fig. 15.2 Mean VAS values in the toxin group (TG) compared to placebo group (PG) at 4 weeks post-injection. Pain reduction in the toxin group is statistically significant ($P = 0.001$). In the toxin group, a total dose of 400 units of aboA was injected into thigh adductors. From Eleopra et al. [70]. Reproduced under creative commons attribution with permission from Toxins and publisher (PMC)

women, 6 men) with knee osteoarthritis. All patients met the clinical and radiological criteria of knee OA. The toxin dose was 250 units diluted with 5 ml of normal saline. The primary outcome measure was the post-injection change in the level of knee pain measured by VAS. The secondary outcome included Knee Injury and Osteoarthritis Outcome Scores, patients' opinion on the change in their knee pain (measured by Persian version of Knee injury and Osteoarthritic Outcome score-KOOS). Primary and secondary outcomes were measured at the baseline and at 4 weeks after injection. At 4 weeks, the KOOS score showed reduction in joint pain and stiffness and severity of symptoms, as well as improvement in quality of life and daily activities (p-values <0.001). Also, there was reduction of pain intensity, joint effusion, knee clicking and locking, and flexion-extension scores (p-values ≤0.005). No serious side effects were noted.

Duran-Hernandez et al. [72] in an open-label study of 35 patients with osteoarthritis of the hip evaluated the efficacy of BoNT-A in reducing hip pain after injecting 500 units of abobotulinumtoxinA into adductor brevis and longus as well as into iliacus muscles. The authors reported at day 90 post-injection significant improvement of referred pain ($P < 0.0001$), rigidity ($P < 0.002$), and mobility as well as external and internal rotation ($P < 0.0001$).

Comparator Studies

Boon et al. [73] compared the efficacy of low dose (100 units) and high dose (200 units) of onabotulinumtoxinA (Botox) with 40 units of methylprednisolone acetate in 60 subjects with pain and functional impairment due to osteoarthritis of the knee. The mean pain score of the studied group was 6 on VAS prior to injection. All study patients had failed to respond previously to pharmacotherapy and physiotherapy**.** The primary outcome was level of reduction of pain in VAS at 8 weeks.

Patients were re-assessed at 26 weeks. Secondary outcomes included quality of life measured by short Form 36, scores of Western Ontario McMaster Arthritis Index (WOMAC) and Patient Global Assessment (in a three question format). All 60 patients completed their 8 weeks evaluation period, while 38 patients had another evaluation at 26 weeks. All three approaches were effective in reducing pain, but the reduction reached significance only for the low dose onA group at 8 weeks ($P = 0.01$). Also, all groups showed a statistically significant decrease in the subsets of pain and stiffness in WOMAC. Side effects were mild and included dry mouth, local swelling and pain at the site of injection, and balance problem. The latter two were more frequent in the high dose onaA group, but the difference between groups did not reach statistical significance.

Sun et al. [74] conducted a single-blind, prospective study comparing the efficacy and safety of onaA with hyaluronate plus rehabilitation in 75 patients with symptomatic ankle osteoarthritis. Of 75 patients, 38 patients received a single injection of 100 units of onaA into the ankle joint, whereas 37 patients had a single injection of hyaluronate plus 12 sessions of physical therapy—patients received physical therapy three times per week for 4 weeks with each session lasting 30 minutes. The primary outcome of the study was the score in Ankle Osteoarthritis Scale (AOS) which includes pain and disability subscales; each measures the intensity on a scale of 0–10. Among the secondary outcomes, the following scales pertained to pain assessment: visual analogue scale (VAS) and global patient satisfaction. Pain-related outcomes were evaluated at baseline (before injection) and at 2 weeks, 1, 3, and 6 months post-injection. The authors considered 30% or more reduction in the pain score as significant. The ankle joint was injected with 100 units of onabotulinumtoxinA. The injecting needle was inserted 1 cm anterior to the distal medial malleolus and advanced posteriorly and slightly superiorly toward the middle of the ankle joint above the talus. If an effusion were present, it was aspirated before injection. After injections, subjects in both groups (onaA and hyaluronate) experienced marked reduction of pain measuring 50% or more in the pain subset of AOS and VAS scores. In the toxin group, the mean baseline VAS value of 4 was reduced to 1.8 at 2 weeks with a further reduction to 1.7 at 3 months. There was, however, no statistically significant difference between the two groups regarding pain relief. Both groups also showed substantial improvement in the disability scores. For some patients, these improvements lasted 6 months. The injections did not induce any significant side effects in either of the two groups.

Mendes et al. [75] compared the efficacy of intra-articular injection of onabotulinumtoxinA (Botox), triamcinolone hexacetonide and saline in 105 patients with knee osteoarthritis. Patients were randomized into three groups each containing 35 patients. Both injector and rater were blinded as to the type and order of injections. Patients' response to treatment was rated by visual analog scale (VAS for pain), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC with pain, stiffness, and function questionnaires), SF36 quality of life questionnaire, 6 min walk test and "time up to go test" at baseline, 4, 8, and 12 weeks after injections. The dose of injected BoNT-A was 100 units and that of triamcinolone was 40 mg. The injected volume was 2 ml for all three interventions. Among all rating

scales employed in this study, only VAS scores for pain showed statistical difference between the three groups. At 4 and 8 weeks post-injection, although both toxin and steroid groups rendered pain relief, VAS scores were significantly lower in the triamcinolone group compared to the BoNT-A group ($P = 0.024$).

Bao et al. [76] compared the efficacy of intra-articular injection of onabotulinumtoxinA with hyaluronate and placebo (saline) in 60 patients with knee osteoarthritis (double-blind, single-center study). There were 20 patients in each group. The injected dose of onaA was 100 units diluted in 2.5 ml of saline. The same volume was used for hyaluronate and saline injections. All three groups also received therapeutic exercise. At 4 and 8 weeks post-injection, the group that received BoNT-A faired better compared to the hyaluronate or saline group on improvement of VAS (pain), WOMAC, and SF36 (quality of life) scores ($P < 0.05$).

Rezasoltani et al. [77] compared the effect of intra-articular BoNT injection with physical therapy alone in 50 patients with knee osteoarthritis. The study was single-blind and randomized. Patients in the toxin group (25) were injected with 100 units of botulinumtoxinA (Dysport). At 4 weeks after injection, both VAS score and Knee Injury and Osteoarthritis Outcome Score (KOOS; including all subscores) were significantly improved compared to the group (25) that received physical therapy alone ($P < 0.05$). There were no side effects.

Shukla et al. [78] compared the effect of intra-articular injection of triamcinolone with a combination of triamcinolone and BoNT-A in 30 patients with chronic osteoarthritis. The injected dose for the BoNT-A was 100 units and for triamcinolone 40 units. Patients were rated by VAS for pain and with Oxford knee score on day 1 and weeks 1, 2, 6, 12, and 26 post-injection. Both groups, after treatment, demonstrated reduced pain and improvement of functional performance. The combined therapy group (15 patients), however, did significantly better than the group that was injected with triamcinolone alone (15 patients). For VAS, the comparative P value reached <0.05 after day 1,= and for Oxford Knee score at 2 weeks post-injection.

Comment

Three double-blind, placebo-controlled studies have assessed the efficacy of botulinum toxins in reducing pain and improving function in chronic osteoarthritis [68–70]. In two studies on knee osteoarthritis, injections were intra-articular [68, 69], whereas in the third study [70], patients with arthritis of the hip joint received toxin and placebo injections into the thigh adductor muscles. In one of the two studies with knee joint injection, the negative results can be challenged based on the presence of a large placebo effect thereby questioning the validity of the results [69]. Based on one class I, positive study [68], the efficacy of intra-articular injection of onabotulinumtoxinA in knee arthritis can be rated as B (probably effective) using the American Academy of Neurology's efficacy assessment criteria [47, 48]. The same level B efficacy (probably effective) applies to injections of

abobotulinumtoxinA into adductor muscles for improving pain in hip osteoarthritis (one class I study [70]). These conclusions are supported by the results of earlier mentioned open-label studies [66, 71, 72].

The published double-blind, placebo-controlled studies that compared the results of intra-articular injection of BoNT and steroid (triamcinolone) have produced controversial results. Although both agents have been shown to reduce joint pain in osteoarthritis, one study demonstrated BoNT-A injection superior to steroid [73], whereas another study noted superiority of triamcinolone [75]. One open-label study has shown that combination of BoNT and triamcinolone injection (intra-articular) is more efficacious than triamcinolone alone in reducing pain in osteoarthritis [78]. In regard to the comparison between intra-articular injection of BoNT and hyaluronate, one double-blind placebo-controlled study (Class I) indicates that BoNT-A is more effective than hyaluronate in reducing arthritic pain and improving the quality of life [76] (level B efficacy, probably more effective).

Botulinum Neurotoxin Treatment after Total Knee Arthroplasty

Chronic, advanced osteoarthritis of the knee is a major source of chronic pain and impaired quality of life in adults with poor response to pharmacotherapy. Total knee arthroplasty (TKA) can improve patients' function and quality of life [79]. Currently, more than 700,000 TKAs are performed in the United States, a figure that is estimated to increase by 143% by year 2050 [80]. Unfortunately, 20–25% of the patients remain unsatisfied with the procedure [81–84]. There is evidence for active contribution of known pain transmitters to the mechanism of pain in TKA. The joint fluid of patients with chronic osteoarthritis who have undergone TKA demonstrates elevated substance P level, a finding that is absent in normal joints [85]. Understandably, novel treatment strategies are welcome in this area of pain medicine since chronic pain after TKA is often refractory to pharmacotherapy.

Singh et al. [86] in a randomized, double-blind, placebo-controlled study investigated the efficacy of intra-articular injection of onabotulinumtoxinA in alleviating chronic pain after TKA. A total of 49 patients participated in the study. The mean age of participants was 67 years, 84% were men, and mean duration of their pain was 4.5 years. All subjects had moderate or severe degrees of pain (rated >6 on 0–10 VAS scale) and their pain duration exceeded 6 months. In the toxin group (23 patients), patients received intra-articular (IA) injections of ona-A, 100 units diluted in 5 cc of 0.9% saline. The control group (26 patients) received 0.5 cc of IA normal saline. The primary outcome in the study was proportion of patients with a decrease of 2 points or more in numerical visual 0–10 scale (VAS) among the patients receiving BoNT-A compared to the placebo group at 2 months post-injection. VAS and McMaster "Osteoarthritic Index Physician Function" were evaluated at baseline

and at 2, 3, and 4 months post-injection. The Patient and Physician Global Impression of Change (PGIC) were also assessed at 2, 3, and 4 months post-injection.

A greater proportion of patients (71%) in the onaA compared to placebo group (35%) experienced reduction in pain assessed by VAS at 2 months post-injection ($p = 0.028$). Duration of meaningful pain relief was 39.6 days (SD 50.4) for onaA group compared to 15.7 days (SD 22.6; $p = 0.045$) for the placebo group. The following outcomes also demonstrated significant differences between onA and placebo group at all assessed times in favor of onaA: Physician Global Assessment of Change ($p = 0.003$); Western Ontario McMaster Osteoarthritis Index physical function ($p = 0.026$), stiffness ($p = 0.004$), and total scores ($p = 0.024$); and Short-Form 36 pain subscale score ($p = 0.049$). No serious side effect related to treatment was noted in the BoNT group. The incidence of other side effects such as local pain after injection and subtle transient weakness around the joint was not statistically different between the two groups.

In a subsequent study, the same authors assessed the effects of repeated injection of onabotulinumtoxinA on pain among patients after knee arthroplasty [87]. Patients who had a good response continued responding after first treatment. Nonresponders did not respond to the second treatment.

Post-TKA flexion contracture develops in hamstring muscles in 15–20% of the patients after TKA [88]. Flexion contractures cause significant tightness in the involved muscles and are often associated with pain and discomfort. In a double-blind, placebo-controlled study, Smith et al. [89] investigated the effect of onabotulinumtoxinA injections upon flexion contracture developed in 14 patients after TKA. BotulinumtoxinA (Botox) or saline was injected into both medial and lateral affected hamstring muscles. The dose of onaA was 50 units per medial and 50 units per lateral hamstring muscle. At one and 6 months post injection, knee extension improved 8 and 5.1 degrees for onaA and 3.8 and 2.2 for saline group, respectively ($P < 0.0001$). No patient reported any serious side effects.

Knee Pain with Vastus Lateralis Imbalance

Anterior knee pain is a common and debilitating ailment with a proposed incidence of 22/1000 individuals per year [89]. Patellofemoral syndrome (PFS) is one of the main causes of chronic knee pain. The affected individuals are usually young, athletic females with no significant knee pathology [90]. Imbalance of vastus muscle has been proposed as one of the leading causes of chronic anterior knee pain [91]. PFS accounts for 12% of referrals to the general orthopedic practice [92]. By electromyography, vastus lateralis muscles show more activity than vastus medialis. Conservative treatments such as orthosis and taping, physiotherapy, and electrical stimulation have modest effects on the patients' anterior knee pain. Long-term studies of PFS have demonstrated that beyond 4–5 years, two-thirds of the patients still have pain and 45% complain of impaired quality of life [93, 94].

Botulinum Toxin Treatment

In 2006, Singer et al. were the first to conduct an open label, clinical trial on a small number of patients ($n = 8$) to assess the efficacy of BoNT therapy in patellofemoral syndrome [95]. The authors injected 300–500 units of abobotulinumtoxinA (Dysport) into the distal part of the vastus lateralis muscle of all patients. Over 12 weeks of observation, patients reported less knee pain and reduced brace dependency as well as increased participation in sports and activities of daily living. Despite development of some degrees of atrophy in vastus lateralis, no appreciable muscle weakness was noted over 24 months of follow-up. In 2011, the same authors [96] conducted a double-blind, placebo-controlled study on 24 patients with anterior knee pain. AbobotulinumtoxinA or saline was injected into the vastus lateralis [VL] muscle. The dose of aboA was 500 units diluted in 4 cc of normal saline. The same volume of normal saline was injected into VL of the control group. All injections into VL were performed under electromyographic guidance. The 4 cc volume in both the toxin and the saline group was distributed into eight sites with 0.5 cc per site. The primary outcomes of the study consisted of changes in knee pain-related disability and activity-related knee pain (measured by VAS) at 3 months post-injection. The BoNT-A-injected group demonstrated a clinically significant reduction in mean pain scores for kneeling (−50.5, $p < 0.001$), stair walking (−20.9, $p < 0.006$), squatting (−30.8, $p < 0.001$), and level walking (−20.3, $p < 0.003$). Placebo subjects demonstrated a reduction in pain for stair walking only (−20.4, not statistically significant $P = 0.097$). The authors concluded that onaA improves anterior knee pain caused by vastus lateralis imbalance.

Chen et al. [97], in an open-label study, prospectively studied the effect of onabotulinumA (onaA) injection on pain and knee function in 12 patients with patellofemoral syndrome. The injected dose was 100 units introduced into the vastus lateralis, 3–5 centimeters above the patella. Patients were rated with Western Ontario and McMaster University Arthritis Index (WOMAC) at the baseline and at 4, 8, and 12 weeks post- injection. Both pain score (20 maximum) and function score (maximum 68) of WOMAC improved significantly over the 12 weeks after onaA injection ($P < 0.05$). The kinetic test showed that following onaA injection, the extension muscle torque also increased, but the values did not reach statistical significance.

In an open-label prospective study, the enduring efficacy of BoNT injection in patellofemoral syndrome and alleviation of anterior knee pain was tested in two cohorts from two different clinics (46 and 53 patients) [98]. A single injection of abobotulinumtoxinA (Dysport) into the vastus lateralis muscle improved the symptoms of PFS in 57 of 65 study participants. On average, the benefit from BoNT therapy lasted 25 months.

Recently, Kersay et al. [99] published the results of a retrospective study of 26 consecutive patients who received BoNT-A injections into vastus lateralis along with physiotherapy for treatment of knee pain caused by patellofemoral syndrome. Vastus lateralis muscle was injected distally at five points (3 cm apart) with a total of 500 units of abobotulinumtoxinA (Dysport). Patients were rated pre- and

post-injection by NRS for pain, QOL (SF-6D) for quality of life and by Kujala and Lysholm questionnaires for functional scores. Patients were followed for a mean of 58.8 ± 36.4 months. There were significant improvements in all the examined parameters after BONT-A injection.

Comments on the Use of BoNT Injections for Pain After Knee Arthroplasty and Vastus Lateralis Imbalance (Patellofemoral Syndrome)

In regard to pain after total knee arthroplasty, the study of Singh et al. [86] qualifies as a class II investigation, hence the efficacy level of toxin therapy for this indication would be C (possibly effective) according to the efficacy criteria set forth by the guidelines of the American Academy of Neurology [47, 48]. The same efficacy rating (C, possibly effective) applies to the use of BoNTs for anterior knee pain in vastus lateralis imbalance (patellofemoral syndrome) based on the availability of one class II study [96]. However, despite this modest evidence, it appears that a trial of botulinum toxin injections is justified for both conditions based on the information from blinded and the abovementioned open-label studies. Patients with chronic TKA and chronic patellofemoral syndrome are desperate for a remedy, and these treatments open a window for potential pain relief. Furthermore, all studies on these two indications have shown a safe profile for BoNT therapy. More blinded, placebo-controlled studies are necessary in order to establish the efficacy of BoNT therapy in these two major pain disorders.

Recent literature has shown that intramuscular BoNT injections close to bone can cause progressive bone loss. This has been clearly demonstrated in the mandibular bone following masseter injections in mice [100]. In mice, the bone loss seems to be dose dependent as doses of 1.2–3.3 units (onaA)/gram do not cause substantial bone loss. In human, repeated injections of botulinum toxins have also been reported to induce bone loss in adjacent bones [101, 102]. Since patients with TKA and patellofemoral syndrome may require repeated injections, the issue of bone loss in human after repetitive BoNT therapy needs further investigation.

References

1. Blanshan N, Krug H. The use of botulinum toxin for the treatment of chronic joint pain: clinical and experimental evidence. Toxins (Basel). 2020;12(5):314. https://doi.org/10.3390/toxins12050314. PMID: 32397671; PMCID: PMC7291335
2. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015–2040. Arthritis Rheumatol. 2016;68:1582–7. https://doi.org/10.1002/art.39692.

3. Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. Nat Rev Rheumatol. 2013;9:654–64. https://doi.org/10.1038/nrrheum.2013.138.
4. Rossetto O, Pirazzini M, Fabris F, Montecucco C. Botulinum neurotoxins: mechanism of action. Handb Exp Pharmacol. 2021;263:35–47. https://doi.org/10.1007/164_2020_355. PMID: 32277300
5. Bach-Rojecky L, Relja M, Lacković Z. Botulinum toxin type A in experimental neuropathic pain. J Neural Transm (Vienna). 2005;112(2):215–9. https://doi.org/10.1007/s00702-004-0265-1. PMID: 15657640
6. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;358:137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 Jul 1. PMID: 28673722
7. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155(4):674–84. https://doi.org/10.1016/j.pain.2013.12.009. Epub 2013 Dec 11. PMID: 24333775; PMCID: PMC3960322
8. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107(1–2):125–33. https://doi.org/10.1016/j.pain.2003.10.008. PMID: 14715398
9. Mika J, Rojewska E, Makuch W, Korostynski M, Luvisetto S, Marinelli S, Pavone F, Przewlocka B. The effect of botulinum neurotoxin A on sciatic nerve injury-induced neuroimmunological changes in rat dorsal root ganglia and spinal cord. Neuroscience. 2011;175:358–66. https://doi.org/10.1016/j.neuroscience.2010.11.040. Epub 2010 Nov 25. PMID: 21111791
10. Bossowska A, Lepiarczyk E, Mazur U, Janikiewicz P, Markiewicz W. Botulinum toxin type A induces changes in the chemical coding of substance P-immunoreactive dorsal root ganglia sensory neurons supplying the porcine urinary bladder. Toxins (Basel). 2015;7(11):4797–816. https://doi.org/10.3390/toxins7114797. PMID: 26580655; PMCID: PMC4663534
11. Wang W, Kong M, Dou Y, Xue S, Liu Y, Zhang Y, Chen W, Li Y, Dai X, Meng J, Wang J. Selective expression of a SNARE-cleaving protease in peripheral sensory neurons attenuates pain-related gene transcription and neuropeptide release. Int J Mol Sci. 2021;22(16):8826. https://doi.org/10.3390/ijms22168826. PMID: 34445536; PMCID: PMC8396265
12. Shin MC, Wakita M, Xie DJ, Yamaga T, Iwata S, Torii Y, Harakawa T, Ginnaga A, Kozaki S, Akaike N. Inhibition of membrane Na+ channels by A type botulinum toxin at femtomolar concentrations in central and peripheral neurons. J Pharmacol Sci. 2012;118(1):33–42. https://doi.org/10.1254/jphs.11060fp. Epub 2011 Dec 10. PMID: 22156364
13. Hong B, Yao L, Ni L, Wang L, Hu X. Antinociceptive effect of botulinum toxin A involves alterations in AMPA receptor expression and glutamate release in spinal dorsal horn neurons. Neuroscience. 2017;357:197–207. https://doi.org/10.1016/j.neuroscience.2017.06.004. Epub 2017 Jun 10. PMID: 28606856
14. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin Type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459. PMID: 31387301; PMCID: PMC6723487
15. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012;61(2):236–9. https://doi.org/10.1016/j.neuint.2012.05.001. Epub 2012 May 8. PMID: 22580329
16. Lacković Z. Botulinum toxin and pain. Handb Exp Pharmacol. 2021;263:251–64. https://doi.org/10.1007/164_2019_348. PMID: 32016565
17. Drinovac Vlah V, Filipović B, Bach-Rojecky L, Lacković Z. Role of central versus peripheral opioid system in antinociceptive and anti-inflammatory effect of botulinum toxin type A in trigeminal region. Eur J Pain. 2018;22(3):583–91. https://doi.org/10.1002/ejp.1146. Epub 2017 Nov 13. PMID: 29134730

18. 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(9):1358–73. https://doi.org/10.1111/j.1526-4610.2011.01990.x. Epub 2011 Aug 29. PMID: 21883197
19. Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC, Aurora SK, Sirimanne M, DeGryse RE, Turkel CC, Dodick DW. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013;331(1–2):48–56. https://doi.org/10.1016/j.jns.2013.05.003. Epub 2013 Jun 19. PMID: 23790235
20. 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(17):1473–8. https://doi.org/10.1212/01.wnl.0000345968.05959.cf. Epub 2009 Feb 25. PMID: 19246421
21. 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(12):1827–33. https://doi.org/10.1111/j.1526-4637.2010.01003.x. PMID: 21134121
22. Childers MK, Wilson DJ, Gnatz SM, Conway RR, Sherman AK. Botulinum toxin type A use in piriformis muscle syndrome: a pilot study. Am J Phys Med Rehabil. 2002;81(10):751–9. https://doi.org/10.1097/00002060-200210000-00006. PMID: 12362115
23. Wu CJ, Lian YJ, Zheng YK, Zhang HF, Chen Y, Xie NC, Wang LJ. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32(6):443–50. https://doi.org/10.1177/0333102412441721. Epub 2012 Apr 5. PMID: 22492424
24. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol. 2016;79(4):569–78. https://doi.org/10.1002/ana.24605. Epub 2016 Feb 16. PMID: 26814620; PMCID: PMC4825405
25. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol. 2008;64(3):274–83. https://doi.org/10.1002/ana.21427. Erratum in: Ann Neurol. 2009 Mar;65(3):359. PMID: 18546285
26. Akalin Ç, Yavuzarslan AB, Akyol C. Efficacy and safety of endoanal ultrasound-guided botulinum toxin in chronic anal fissure. Am Surg. 2021;27:31348211034750. https://doi.org/10.1177/00031348211034750. Epub ahead of print. PMID: 34313489
27. Torkamand F, Mirjavadi SJ, Khatami F, Guitynavard F, Aghamir SMK. Evaluation of several botulinum toxins-A delivering systems into the bladder in interstitial cystitis/painful bladder syndrome (IC/PBS). Am J Clin Exp Urol. 2019;7(5):346–51. PMID: 31763366; PMCID: PMC6872472
28. 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(9):649–54. https://doi.org/10.1097/01.phm.0000176339.73591.d7. PMID: 16141740
29. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes - an evidence based review. Toxicon. 2018;147:120–8. https://doi.org/10.1016/j.toxicon.2018.01.017. Epub 2018 Feb 1. PMID: 29409817
30. Degen RM, Conti MS, Camp CL, Altchek DW, Dines JS, Werner BC. Epidemiology and disease burden of lateral epicondylitis in the USA: analysis of 85,318 patients. HSS J. 2018;14(1):9–14. https://doi.org/10.1007/s11420-017-9559-3. Epub 2017 Jun 5. PMID: 29398988; PMCID: PMC5786580
31. Hamilton PG. The prevalence of humeral epicondylitis: a survey in general practice. J R Coll Gen Pract. 1986;36(291):464–5. PMID: 3440991; PMCID: PMC1960610
32. Verhaar JA. Tennis elbow. Anatomical, epidemiological and therapeutic aspects. Int Orthop. 1994;18(5):263–7. https://doi.org/10.1007/BF00180221. PMID: 7852001
33. Solheim E, Hegna J, Øyen J. Arthroscopic versus open tennis elbow release: 3- to 6-year results of a case-control series of 305 elbows. Arthroscopy. 2013;29(5):854–9. https://doi.org/10.1016/j.arthro.2012.12.012. Epub 2013 Feb 4. PMID: 23388420

34. Nirschl RP, Ashman ES. Elbow tendinopathy: tennis elbow. Clin Sports Med. 2003;22(4):813–36. https://doi.org/10.1016/s0278-5919(03)00051-6. PMID: 14560549
35. Connell D, Burke F, Coombes P, McNealy S, Freeman D, Pryde D, Hoy G. Sonographic examination of lateral epicondylitis. AJR Am J Roentgenol. 2001;176(3):777–82. https://doi.org/10.2214/ajr.176.3.1760777. PMID: 11222225
36. Linnanmäki L, Kanto K, Karjalainen T, Leppänen OV, Lehtinen J. Platelet-rich plasma or autologous blood do not reduce pain or improve function in patients with lateral epicondylitis: a randomized controlled trial. Clin Orthop Relat Res. 2020;478(8):1892–900. https://doi.org/10.1097/CORR.0000000000001185. PMID: 32732573; PMCID: PMC7371073
37. Zhou Y, Guo Y, Zhou R, Wu P, Liang F, Yang Z. Effectiveness of acupuncture for lateral epicondylitis: a systematic review and meta-analysis of randomized controlled trials. Pain Res Manag. 2020;2020 Mar 20:8506591. https://doi.org/10.1155/2020/8506591. PMID: 32318130; PMCID: PMC7114772
38. Yao G, Chen J, Duan Y, Chen X. Efficacy of extracorporeal shock wave therapy for lateral epicondylitis: a systematic review and meta-analysis. Biomed Res Int. 2020;2020:2064781. https://doi.org/10.1155/2020/2064781. PMID: 32309425; PMCID: PMC7106907
39. Acosta-Olivo CA, Millán-Alanís JM, Simental-Mendía LE, Álvarez-Villalobos N, Vilchez-Cavazos F, Peña-Martínez VM, Simental-Mendía M. Effect of normal saline injections on lateral epicondylitis symptoms: a systematic review and meta-analysis of randomized clinical trials. Am J Sports Med. 2020;48(12):3094–102. https://doi.org/10.1177/0363546519899644. Epub 2020 Feb 11. PMID: 32045280
40. Krogh TP, Bartels EM, Ellingsen T, Stengaard-Pedersen K, Buchbinder R, Fredberg U, Bliddal H, Christensen R. Comparative effectiveness of injection therapies in lateral epicondylitis: a systematic review and network meta-analysis of randomized controlled trials. Am J Sports Med. 2013;41(6):1435–46. https://doi.org/10.1177/0363546512458237. Epub 2012 Sep 12. PMID: 22972856
41. Behazin M, Kachooei AR. Arthroscopic recession technique in the surgery of tennis elbow by sharp cutting the Extensor Carpi radialis Brevis (ECRB) tendon origin. Arch Bone Jt Surg. 2021;9(2):174–9. https://doi.org/10.22038/abjs.2020.48173.2383. PMID: 34026934; PMCID: PMC8121031
42. Wong SM, Hui AC, Tong PY, Poon DW, Yu E, Wong LK. Treatment of lateral epicondylitis with botulinum toxin: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2005;143(11):793–7. https://doi.org/10.7326/0003-4819-143-11-200512060-00007. PMID: 16330790
43. Hayton MJ, Santini AJ, Hughes PJ, Frostick SP, Trail IA, Stanley JK. Botulinum toxin injection in the treatment of tennis elbow. A double-blind, randomized, controlled, pilot study. J Bone Joint Surg Am. 2005;87(3):503–7. https://doi.org/10.2106/JBJS.D.01896. PMID: 15741614
44. Placzek R, Drescher W, Deuretzbacher G, Hempfing A, Meiss AL. Treatment of chronic radial epicondylitis with botulinum toxin A. A double-blind, placebo-controlled, randomized multicenter study. J Bone Joint Surg Am. 2007;89(2):255–60. https://doi.org/10.2106/JBJS.F.00401. PMID: 17272437
45. Espandar R, Heidari P, Rasouli MR, Saadat S, Farzan M, Rostami M, Yazdanian S, Mortazavi SM. Use of anatomic measurement to guide injection of botulinum toxin for the management of chronic lateral epicondylitis: a randomized controlled trial. CMAJ. 2010;182(8):768–73. https://doi.org/10.1503/cmaj.090906. Epub 2010 Apr 26. PMID: 20421357; PMCID: PMC2871199
46. Creuzé A, Petit H, de Sèze M. Short-term effect of low-dose, electromyography-guided botulinum toxin a injection in the treatment of chronic lateral epicondylar tendinopathy: a randomized, double-blinded study. J Bone Joint Surg Am. 2018;100(10):818–26. https://doi.org/10.2106/JBJS.17.00777. PMID: 29762276

47. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology. 2008;71(20):1639–43. https://doi.org/10.1212/01.wnl.0000336535.27773.c0. PMID: 19001255
48. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008;71(20):1634–8. https://doi.org/10.1212/01.wnl.0000336533.19610.1b. PMID: 19001254
49. Lin YC, Tu YK, Chen SS, Lin IL, Chen SC, Guo HR. Comparison between botulinum toxin and corticosteroid injection in the treatment of acute and subacute tennis elbow: a prospective, randomized, double-blind, active drug-controlled pilot study. Am J Phys Med Rehabil. 2010;89(8):653–9. https://doi.org/10.1097/PHM.0b013e3181cf564d. PMID: 20134306
50. Guo YH, Kuan TS, Chen KL, Lien WC, Hsieh PC, Hsieh IC, Chiu SH, Lin YC. Comparison between steroid and 2 different sites of botulinum toxin injection in the treatment of lateral epicondylalgia: a randomized, double-blind, active drug-controlled pilot study. Arch Phys Med Rehabil. 2017;98(1):36–42. https://doi.org/10.1016/j.apmr.2016.08.475. Epub 2016 Sep 22. PMID: 27666156
51. Keizer SB, Rutten HP, Pilot P, Morré HH, v Os JJ, Verburg AD. Botulinum toxin injection versus surgical treatment for tennis elbow: a randomized pilot study. Clin Orthop Relat Res 2002;(401):125–131. https://doi.org/10.1097/00003086-200208000-00015. PMID: 12151889.
52. Lee SH, Choi HH, Chang MC. The effect of botulinum toxin injection into the common extensor tendon in patients with chronic lateral epicondylitis: a randomized trial. Pain Med. 2020;21(9):1971–6. https://doi.org/10.1093/pm/pnz323. PMID: 31804698
53. Galván Ruiz A, Vergara Díaz G, Rendón Fernández B, Echevarría Ruiz De Vargas C. Effects of ultrasound-guided Administration of botulinum toxin (IncobotulinumtoxinA) in patients with lateral epicondylitis. Toxins (Basel). 2019;11(1):46. https://doi.org/10.3390/toxins11010046. PMID: 30650587; PMCID: PMC6356468
54. Morré HH, Keizer SB, van Os JJ. Treatment of chronic tennis elbow with botulinum toxin. Lancet. 1997;349(9067):1746. https://doi.org/10.1016/s0140-6736(05)62958-3. PMID: 9193392
55. Lim EC, Seet RC, Cheah AE, Lim AY. Injection of botulinum toxin to the extensor carpi radialis brevis for tennis elbow. J Hand Surg Eur Vol. 2010;35(5):425–6. https://doi.org/10.1177/1753193409349844. PMID: 20515991
56. Song B, Day D, Jayaram P. Efficacy of botulinum toxin in treating lateral epicondylitis-does injection location matter?: a systematic review. Am J Phys Med Rehabil. 2020;99(12):1157–63. https://doi.org/10.1097/PHM.0000000000001511. PMID: 33214499
57. Dong W, Goost H, Lin XB, Burger C, Paul C, Wang ZL, Kong FL, Welle K, Jiang ZC, Kabir K. Injection therapies for lateral epicondylalgia: a systematic review and Bayesian network meta-analysis. Br J Sports Med. 2016;50(15):900–8. https://doi.org/10.1136/bjsports-2014-094387. Epub 2015 Sep 21. PMID: 26392595
58. Kim GM, Yoo SJ, Choi S, Park YG. Current trends for treating lateral epicondylitis. Clin Shoulder Elb. 2019;22(4):227–34. https://doi.org/10.5397/cise.2019.22.4.227. PMID: 33330224; PMCID: PMC7714311
59. Grüner S, Schulz A, Schlüter-Brust K, Lippert-Grüner M. Botulinum toxin for chronic lateral epicondylitis (LE). Z Orthop Unfall. 2021;159(5):554–564. English, German. https://doi.org/10.1055/a-1202-6220. Epub 2020 Aug 3. PMID: 32746490.
60. Quicke JG, Conaghan PG, Corp N, Peat G. Osteoarthritis year in review 2021: epidemiology & therapy. Osteoarthr Cartil. 2021:S1063–4584(21)00934–1. https://doi.org/10.1016/j.joca.2021.10.003. Epub ahead of print. PMID: 34695571.
61. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. Pain Med. 2012;13(6):740–53. https://doi.org/10.1111/j.1526-4637.2012.01394.x. Epub 2012 May 23. PMID: 22621287; PMCID: PMC3376243
62. Yurtbay A, Say F, Çinka H, Ersoy A. Multiple platelet-rich plasma injections are superior to single PRP injections or saline in osteoarthritis of the knee: the 2-year results of a randomized,

double-blind, placebo-controlled clinical trial. Arch Orthop Trauma Surg. 2021; https://doi.org/10.1007/s00402-021-04230-2. Epub ahead of print. PMID: 34705072

63. Bettonville M, Léon M, Margaux J, Urbin-Choffray D, Theunissen E, Besse-Hammer T, Fortems Y, Verlinden S, Godeaux O, Delmarcelle AS, Kaux JF. Safety and efficacy of a single intra-articular injection of a novel enhanced protein solution (JTA-004) compared to hylan G-F 20 in symptomatic knee osteoarthritis: a randomized, double-blind, controlled phase II/III study. BMC Musculoskelet Disord. 2021;22(1):888. https://doi.org/10.1186/s12891-021-04750-3. PMID: 34666767; PMCID: PMC8527807
64. Chen HH, Chen YC, Yu SN, Lai WL, Shen YS, Shen PC, Lin SH, Chang CH, Lee SM. Infrapatellar fat pad-derived mesenchymal stromal cell product for treatment of knee osteoarthritis: a first-in-human study with evaluation of the potency marker. Cytotherapy. 2021;22:1377. https://doi.org/10.1016/j.jcyt.2021.08.006. Epub ahead of print. PMID: 34696962
65. Lee E, Padgett B. Intra-articular injection of BPC 157 for multiple types of knee pain. Altern Ther Health Med. 2021;27(4):8–13. PMID: 34324435
66. Mahowald ML, Singh JA, Dykstra D. Long term effects of intra-articular botulinum toxin A for refractory joint pain. Neurotox Res. 2006;9(2–3):179–88. https://doi.org/10.1007/BF03033937. PMID: 16785116
67. Castiglione A, Bagnato S, Boccagni C, Romano MC, Galardi G. Efficacy of intra-articular injection of botulinum toxin type A in refractory hemiplegic shoulder pain. Arch Phys Med Rehabil. 2011;92(7):1034–7. https://doi.org/10.1016/j.apmr.2011.01.015. PMID: 21704782
68. McAlindon TE, Schmidt U, Bugarin D, Abrams S, Geib T, DeGryse RE, Kim K, Schnitzer TJ. Efficacy and safety of single-dose onabotulinumtoxinA in the treatment of symptoms of osteoarthritis of the knee: results of a placebo-controlled, double-blind study. Osteoarthr Cartil. 2018;26(10):1291–9. https://doi.org/10.1016/j.joca.2018.05.001. Epub 2018 May 9. PMID: 29753118
69. Arendt-Nielsen L, Jiang GL, DeGryse R, Turkel CC. Intra-articular onabotulinumtoxinA in osteoarthritis knee pain: effect on human mechanistic pain biomarkers and clinical pain. Scand J Rheumatol. 2017;46(4):303–16. https://doi.org/10.1080/03009742.2016.1203988. Epub 2016 Oct 13. PMID: 27733091
70. Eleopra R, Rinaldo S, Lettieri C, Santamato A, Bortolotti P, Lentino C, Tamborino C, Causero A, Devigili G. AbobotulinumtoxinA: a new therapy for hip osteoarthritis. A prospective randomized double-blind multicenter study. Toxins (Basel). 2018;10(11):448. https://doi.org/10.3390/toxins10110448. PMID: 30384438; PMCID: PMC6266300
71. Najafi S, Sanati E, Khademi M, Abdorrazaghi F, Mofrad RK, Rezasoltani Z. Intra-articular botulinum toxin type A for treatment of knee osteoarthritis: clinical trial. Toxicon. 2019;165:69–77. https://doi.org/10.1016/j.toxicon.2019.04.003. Epub 2019 Apr 14. PMID: 30995453
72. Durán-Hernández S, Soto-Rodríguez JF, Allen-Bobadilla J, Durán-Hernández N, García-Mosco P. Osteoarthritis of the hip conservative treatment with type A botulinum toxin. Gac Med Mex. 2019;155(Suppl 1):S44–8. https://doi.org/10.24875/GMM.M19000289. PMID: 31638614
73. Boon AJ, Smith J, Dahm DL, Sorenson EJ, Larson DR, Fitz-Gibbon PD, Dykstra DD, Singh JA. Efficacy of intra-articular botulinum toxin type A in painful knee osteoarthritis: a pilot study. PM R. 2010;2(4):268–76. https://doi.org/10.1016/j.pmrj.2010.02.011. PMID: 20430328
74. Sun SF, Hsu CW, Lin HS, Chou YJ, Chen JY, Wang JL. Efficacy of intraarticular botulinum toxin A and intraarticular hyaluronate plus rehabilitation exercise in patients with unilateral ankle osteoarthritis: a randomized controlled trial. J Foot Ankle Res. 2014;7(1):9. https://doi.org/10.1186/1757-1146-7-9. PMID: 24502534; PMCID: PMC3922455
75. Mendes JG, Natour J, Nunes-Tamashiro JC, Toffolo SR, Rosenfeld A, Furtado RNV. Comparison between intra-articular Botulinum toxin type A, corticosteroid, and saline

in knee osteoarthritis: a randomized controlled trial. Clin Rehabil. 2019;33(6):1015–26. https://doi.org/10.1177/0269215519827996. Epub 2019 Feb 19. PMID: 30782000
76. Bao X, Tan JW, Flyzik M, Ma XC, Liu H, Liu HY. Effect of therapeutic exercise on knee osteoarthritis after intra-articular injection of botulinum toxin type A, hyaluronate or saline: a randomized controlled trial. J Rehabil Med. 2018;50(6):534–41. https://doi.org/10.2340/16501977-2340. PMID: 29664106
77. Rezasoltani Z, Dadarkhah A, Tabatabaee SM, Abdorrazaghi F, Kazempour Mofrad M, Kazempour MR. Therapeutic effects of intra-articular botulinum neurotoxin versus physical therapy in knee osteoarthritis. Anesth Pain Med. 2021;11(3):e112789. https://doi.org/10.5812/aapm.112789. PMID: 34540630; PMCID: PMC8438713.
78. Shukla D, Sreedhar SK, Rastogi V. A comparative study of botulinum toxin: a with triamcinolone compared to triamcinolone alone in the treatment of osteoarthritis of knee. Anesth Essays Res. 2018;12(1):47–9. https://doi.org/10.4103/aer.AER_210_17. PMID: 29628553; PMCID: PMC5872892
79. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, Rasmussen S. A randomized, controlled trial of total knee replacement. N Engl J Med. 2015;373(17):1597–606. https://doi.org/10.1056/NEJMoa1505467. PMID: 26488691
80. Inacio MCS, Paxton EW, Graves SE, Namba RS, Nemes S. Projected increase in total knee arthroplasty in the United States - an alternative projection model. Osteoarthr Cartil. 2017;25(11):1797–803. https://doi.org/10.1016/j.joca.2017.07.022. Epub 2017 Aug 8. PMID: 28801208
81. Lange JK, Lee YY, Spiro SK, Haas SB. Satisfaction rates and quality of life changes following total knee arthroplasty in age-differentiated cohorts. J Arthroplast. 2018;33(5):1373–8. https://doi.org/10.1016/j.arth.2017.12.031. Epub 2017 Dec 29. PMID: 29395722
82. Anderson JG, Wixson RL, Tsai D, Stulberg SD, Chang RW. Functional outcome and patient satisfaction in total knee patients over the age of 75. J Arthroplast. 1996;11(7):831–40. https://doi.org/10.1016/s0883-5403(96)80183-5. PMID: 8934323
83. Baker PN, van der Meulen JH, Lewsey J. Gregg PJ; National Joint Registry for England and Wales. The role of pain and function in determining patient satisfaction after total knee replacement. Data from the National Joint Registry for England and Wales. J Bone Joint Surg Br. 2007;89(7):893–900. https://doi.org/10.1302/0301-620X.89B7.19091. PMID: 17673581
84. Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. Pain. 2011;152(3):566–72. https://doi.org/10.1016/j.pain.2010.11.023. Epub 2011 Jan 15. PMID: 21239114
85. Pritchett JW. Substance P level in synovial fluid may predict pain relief after knee replacement. J Bone Joint Surg Br. 1997;79(1):114–6. https://doi.org/10.1302/0301-620x.79b1.6807. PMID: 9020458
86. 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. https://doi.org/10.3899/jrheum.100336. Epub 2010 Sep 1. Erratum in: J Rheumatol. 2011 Jul;38(7):1534. PMID: 20810509; PMCID: PMC3018709.
87. Singh JA. Efficacy of long-term effect and repeat intraarticular botulinum toxin in patients with painful Total joint arthroplasty: a retrospective study. Br J Med Med Res. 2014;4(1):139–48. https://doi.org/10.9734/BJMMR/2014/4897. PMID: 24319672; PMCID: PMC3850174
88. Bong MR, Di Cesare PE. Stiffness after total knee arthroplasty. J Am Acad Orthop Surg. 2004;12(3):164–71. https://doi.org/10.5435/00124635-200405000-00004. PMID: 15161169
89. Smith EB, Shafi KA, Greis AC, Maltenfort MG, Chen AF. Decreased flexion contracture after total knee arthroplasty using Botulinum toxin A: a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc. 2016;24(10):3229–34. https://doi.org/10.1007/s00167-016-4277-9. Epub 2016 Aug 11. PMID: 27515301
90. Boling M, Padua D, Marshall S, Guskiewicz K, Pyne S, Beutler A. Gender differences in the incidence and prevalence of patellofemoral pain syndrome. Scand J Med Sci Sports.

2010;20(5):725–30. https://doi.org/10.1111/j.1600-0838.2009.00996.x. PMID: 19765240; PMCID: PMC2895959

91. Petersen W, Ellermann A, Gösele-Koppenburg A, Best R, Rembitzki IV, Brüggemann GP, Liebau C. Patellofemoral pain syndrome. Knee Surg Sports Traumatol Arthrosc. 2014;22(10):2264–74. https://doi.org/10.1007/s00167-013-2759-6. Epub 2013 Nov 13. PMID: 24221245; PMCID: PMC4169618
92. Powers CM. Patellar kinematics, part I: the influence of vastus muscle activity in subjects with and without patellofemoral pain. Phys Ther. 2000;80(10):956–64. PMID: 11002431
93. Rathleff MS, Rasmussen S, Olesen JL. Utilfredsstillende langtidsresultater efter konservativ behandling af patellofemoralt smertesyndrom [Unsatisfactory long-term prognosis of conservative treatment of patellofemoral pain syndrome]. Ugeskr Laeger. 2012;174(15):1008–13. Danish. PMID: 22487407
94. Stathopulu E, Baildam E. Anterior knee pain: a long-term follow-up. Rheumatology (Oxford). 2003;42(2):380–2. https://doi.org/10.1093/rheumatology/keg093. PMID: 12595641
95. Singer BJ, Silbert PL, Dunne JW, Song S, Singer KP. An open label pilot investigation of the efficacy of Botulinum toxin type A [Dysport] injection in the rehabilitation of chronic anterior knee pain. Disabil Rehabil. 2006;28(11):707–13. https://doi.org/10.1080/09638280500301477. PMID: 16809213
96. Singer BJ, Silbert PL, Song S, Dunne JW, Singer KP. 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. Br J Sports Med. 2011;45(8):640–5. https://doi.org/10.1136/bjsm.2009.069781. Epub 2010 Apr 23. PMID: 20418523; PMCID: PMC3106976.
97. Chen JT, Tang AC, Lin SC, Tang SF. Anterior knee pain caused by patellofemoral pain syndrome can be relieved by Botulinum toxin type A injection. Clin Neurol Neurosurg. 2015;129(Suppl 1):S27–9. https://doi.org/10.1016/S0303-8467(15)30008-1. PMID: 25683309
98. Silbert BI, Singer BJ, Silbert PL, Gibbons JT, Singer KP. Enduring efficacy of Botulinum toxin type A injection for refractory anterior knee pain. Disabil Rehabil. 2012;34(1):62–8. https://doi.org/10.3109/09638288.2011.587084. Epub 2011 Sep 22. PMID: 21936736
99. Kesary Y, Singh V, Frenkel-Rutenberg T, Greenberg A, Dekel S, Schwarzkopf R, Snir N. Botulinum toxin injections as salvage therapy is beneficial for management of patellofemoral pain syndrome. Knee Surg Relat Res. 2021;33(1):39. https://doi.org/10.1186/s43019-021-00121-3. PMID: 34715941
100. Balanta-Melo J, Toro-Ibacache V, Kupczik K, Buvinic S. Mandibular bone loss after masticatory muscles intervention with botulinum toxin: an approach from basic research to clinical findings. Toxins (Basel). 2019;11(2):84. https://doi.org/10.3390/toxins11020084. PMID: 30717172; PMCID: PMC6409568
101. Lee HJ, Kim SJ, Lee KJ, Yu HS, Baik HS. Repeated injections of botulinum toxin into the masseter muscle induce bony changes in human adults: a longitudinal study. Korean J Orthod. 2017;47(4):222–8. https://doi.org/10.4041/kjod.2017.47.4.222. Epub 2017 May 26. PMID: 28670563; PMCID: PMC5466904
102. Raphael KG, Tadinada A, Bradshaw JM, Janal MN, Sirois DA, Chan KC, Lurie AG. Osteopenic consequences of botulinum toxin injections in the masticatory muscles: a pilot study. J Oral Rehabil. 2014;41(8):555–63. https://doi.org/10.1111/joor.12180. Epub 2014 May 17. PMID: 24836732

Chapter 16
Botulinum Toxin in Dentistry and Treatment of Chronic Orofacial Pain

Shahroo Etemad-Moghadam, Mojgan Alaeddini, and Bahman Jabbari

Introduction

Pain, either acute or chronic, is a disturbing uncomfortable sensation with multiple aspects that afflicts individuals at different mental, psychological, and physiological levels [1]. Orofacial pain (OFP) is described as pain involving the hard and soft tissues of the face and all its related areas including the oral cavity [2]. In contrast to the acute type which is temporary, chronic pain does not subside after removal of a stimulus or healing of the injured region and is considered a disease by its very nature [1]. Pain persisting beyond 3 months is considered as chronic, which is a relatively common issue, affecting approximately 20% of people worldwide [3]. In the orofacial region, its prevalence is between 16.1% and 33.2%, with 10% qualifying as chronic [4]. Considering the distinctive anatomical, functional, and physiological features of the orofacial complex, in addition to the social and psychological elements associated with OFP, there is a strong need for further research in this area in order to introduce safe and effective treatment options to achieve optimal management strategies.

Chronic headaches and OFP are among the most common pain disorders known to clinicians. They have been classified by several systems and were included

The original version of this chapter was revised. The correction to this chapter is available at https://doi.org/10.1007/978-3-030-99650-5_21

S. Etemad-Moghadam (✉)· M. Alaeddini
Dental Research Center, Dentistry Research Institute, Tehran University of Medical Sciences, Tehran, Iran
e-mail: etemadmo@sina.tums.ac.ir

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

Clinical Professor of Neurology, University of California, Irvine, CA, USA
e-mail: bahman.jabbari@yale.edu

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_16

separately in the most recent version of the International Classification of Diseases (ICD-11), taking effect as of January 2022 [3, 5]. Generally, chronic OFP has been divided into musculoskeletal, neuropathic, neurovascular, and idiopathic subtypes with differing nomenclature used in different classification systems [1, 6–8]. Regarding the versatile mode of action of botulinum neurotoxin (BoNT), with its anticholinergic, analgesic, and anti-inflammatory effects, this toxin can be a safe and appealing option for treating diseases in each of these subclasses.

Adopting the style used by the International Classification of Headache Disorders, 3rd edition (ICHD-3) and aligned with ICD-11, the International Classification of Orofacial Pain (ICOP) has offered a detailed and elaborate classification with practical diagnostic guidelines [9] and has been used in most sections of the following text, where possible.

Chronic Orofacial Pain

Musculoskeletal Orofacial Pain

Chronic musculoskeletal pain arises from disorders or causes that involve bones, joints, muscles, and soft tissues [8]. Most facial pains have a musculoskeletal origin and encompass the area innervated by the maxillary and mandibular branches of the trigeminal nerve [5]. To describe this type of pain, terms like “deep,” “pressure,” “muscle tenderness,” and “dysfunction” have been used [7]. Conditions belonging to this subclass include masticatory myofascial pain, temporomandibular joint pain, tension-type headache, and cervical headache [6, 7]. The following text will concentrate on the two first subtypes, which will be presented collectively under the more recognized term, temporomandibular disorders (TMDs).

Temporomandibular Disorders (TMDs)

Definition, Classification, and Epidemiology

The term TMD refers to a group of painful and non-painful disorders involving the temporomandibular joint (TMJ), masticatory muscles, and adjoining structures [9]. It has been estimated that approximately 33% of the general population demonstrate at least one TMD symptom, that is, masticatory muscle tenderness and/or pain, TMJ sounds and/or pain, and restricted jaw opening [10]. Painful TMDs are the most common cause of OFP, and their annual incidence in the United States has been reported at 4%. They occur twice as often in women as in men and are more common in the second to fifth decades of life. Persistent pain has been reported in 49% of TMD patients [11]. Association with other comorbidities like migraine/headache, neck pain, fibromyalgia, irritable bowel, and lower back pain is not uncommon [12, 13].

According to ICOP, pain related to TMD can be found under myofascial OFP and TMJ pain [9]. The diagnostic criteria for myofascial OFP start with the initial

distinction between the two main subtypes: primary and secondary myofascial OFP, followed by further subdivisions, subtypes, and subclasses. Masticatory muscle pain, not assignable to another disorder, is considered "primary," while myofascial pain due to tendonitis, myositis, or muscle spasm is regarded as "secondary." Primary masticatory muscle pain can be episodic (30 min each and a total duration of ≥2 h/day) or continual/continuous and manifest in the jaw, temple, and ear vicinity. Its occurrence in the temporalis and/or masseter muscles needs to be confirmed by examination and should be provoked by palpation of one or both of these muscles and/or movements related to maximum jaw opening. It must also exhibit an increase or decrease in pain, following jaw movement, function, or parafunction [9]. Provocation of pain is determined by exertion of 1 kg pressure for 2 s, and referral or spread of pain is assessed through applying palpation pressure of 1 kg for 5 s [14].

Similarly, the diagnostic criteria for TMJ pain also include initially differentiating between primary and secondary subtypes, followed by further classification into comparable subtypes and subclasses. Primary TMJ pain is localized to the joint without any causative disorder and can occur with or without jaw movement or palpation. It involves episodic or constant pain inside and/or in front of the ear confirmed by examination indicating occurrence in one or both TMJs. It also should be provoked by palpation of the lateral pole of the condyle or its vicinity and/or by maximum jaw movement of any type, with modification of pain. Secondary TMJ pain is caused by other disorders like systemic or nonsystemic arthritis, degenerative joint disease, subluxation, or disc displacement with or without reduction and the possibility of intermittent locking [9].

Management of Temporomandibular Disorders

The treatment of TMD has a long history evolving from orthodontics for occlusion correction in the late 1990s to more invasive techniques like arthrocentesis or arthroscopy in early 2000 to physical, psychological, and pharmacological therapies during the past decade [15]. Injection of substances such as corticosteroids, hyaluronate, anesthetics, and BoNT is reserved for patients whose pain does not resolve after conservative treatments like counseling, medication, physiotherapy, and occlusal splints [15, 16]. Traditionally, BoNT has been administered intramuscularly for muscle relaxation leading to bite strength reduction and an indirect "joint-sparing effect" with consequent pain relief [17]. More recent evidence suggests axonal transport of BoNT to motor and sensory neurons from the peripheral to the central nervous system (CNS). Clinically, the antinociceptive effect of intramuscular BoNT injection is felt before muscle paralysis. Following soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) cleavage by BoNT at the injection site, there are significant reductions in inflammatory factors like IL-1ß, calcitonin gene-related peptide, and substance P [10, 18], making BoNT practical for short- and long-term TMD pain management.

In cases where TMD pain is related to TMJ issues, BoNT can decrease TMJ overload by relieving muscle tension, could be administered to treat cases associated with dislocations [19], and may be directly injected in the joint to exert an antinociceptive effect by blocking neurotransmitter release from primary sensory neurons [20]. Neuropeptides and cytokines in inflamed joints sensitize the local nerves. Pain relief in arthritis occurs following reduction of inflammation due to

neuropeptide inhibition. Intra-articular BoNT injection may have an anti-inflammatory effect through inhibition of neuropeptides/cytokines, reducing generation of its mediators like substance P, ultimately leading to diminished pain [21].

Efficacy of BoNT in the Treatment of Temporomandibular Disorders with Pain

BoNT Injection for TMD Pain Primarily Attributed to the Masticatory Muscles

Inactivation of neural transmission and acetylcholine blocking are BoNT features that have led to its approval for treating a variety of muscle disorders. In the orofacial region, the anti-inflammatory, muscle-weakening, and analgesic effects of this toxin have been exploited to treat TMD pain [22, 23].

Using the criteria of the American Academy of Neurology (AAN) [24, 25], the efficacy of BoNT-A in TMD-associated myofascial pain management can be given a Level B efficacy (*"probably effective"*) based on one class I study [23] and one recent class II trial [22].

The most recent high-quality, class II study is a randomized clinical trial by de la Torre Canales et al. [22], who evaluated the effectiveness and safety of BoNT-A in 100 women with persistent myofascial pain (47 had arthralgia or disc displacement in addition to myofascial pain). Five groups of 20 patients each received oral appliance, placebo, 80 U, 140 U, or 200 U onabotulinumtoxinA (Botox). All injections for subjects allocated to placebo/BoNT groups were administered in both masseter and temporalis muscles by an operator blind to the dilutions. Based on the results, the three doses of BoNT-A significantly decreased pain compared to placebo and were all as effective as oral appliances.

Using different quality assessment approaches like GRADE and Jadad, a number of systematic reviews/meta-analyses have reported the evidence of BoNT utility for TMD pain control to be moderate to low, and despite demonstrating improvements in patients, its efficacy has been stated to be unclear at the current time. The risk of side effects was reported as not significant. According to these reviews, some investigations support the better performance of BoNT compared to placebo in the short-term (1 month) follow-up, but not during longer intervals (3 and 6 months); a number of studies have reported BoNT to be equal to or slightly better than other treatment modalities, and yet others report no significant difference compared to controls or therapies like facial manipulation [26–28].

From 2017, among the investigations on BoNT efficacy in TMD pain, we analyzed nine studies that were either high quality [22, 23] and/or had used the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [14] for their patient selection [18, 22, 29–34]. To further minimize heterogeneity, TMD due to bruxism will be discussed separately, especially considering that not all patients with TMD have bruxism and vice versa [35]. There were three randomized trials, and the rest were either retrospective or prospective clinical studies (Table 16.1). A variety of BoNT doses, injection sites and numbers, assessment tools, and patient groups were reported. Injections ranged from 30 MU Botox injected into one to six muscles [30] to 200 U Botox injected into 20 sites in four muscles [22]. The shortest lasting effect was 30 days [18], while two studies reported longer relief periods of up to 6 months [22, 32].

Table 16.1 Outline of studies using botulinum toxin to manage myofascial pain related to temporomandibular disorders

Author/ year	Study type	Patients	BoNT	Dose	Injection	Assessment	Outcome	Diagnosis	Comments
Khawaja et al. 2017 [29]	Retrospective	$N = 116$	Botox (onaA)	100U	In painful muscles (masseter±temporalis); 2 cycles ≥12 w apart	11-point Likert-type scale	Sg pain relief for 10 w in 1/3 of patients	Refractory masticatory myalgia	Patients with Sg relief had Sg more AE
Abboud et al. 2017 [30]	Retrospective	$N = 25$ Localized: 13 Referring: 12	Botox	30–180 MU	Into 1–6 uni/bilateral painful muscles: masseter, anterior temporalis, sternocleidomastoid, and posterior digastric	Self-reported pain evaluation	Sg benefit of BoNT in patients with localized, but not referring MFP	MFP	AE: transient tenderness, asymmetric smile
Patel et al. 2017 [23]	Randomized controlled pilot	$N = 19$; Plc: 9 BoNT: 10	Xeomin (incoA)	170U	2 masseter (100U), 2 temporalis (50U), 2 external pterygoid muscle (20)	0–10 pain scale	Sg decrease of pain scores vs placebo	TMD	No adverse effects
Villa et al. 2018 [31]	Retrospective	$N = 28$	Botox	150U	2 masseter (100U) in 3 sites, and 2 temporalis (50U) in two sites	VAS (pain) OHIP-14 TMJ-QoL	- Sg decrease in VAS - Sg improved QoL	TMD	Sg effects seen in 1st and 3rd month
Montes-Carmona et al. 2020 [32]	Randomized, single-center clinical trial	$N = 60$ (20×3); Plc, lidocaine, BoNT	Botox	2 masseter: 48–60U 2 temporalis: 48U 2 lateral pterygoid: 16U 2 medial pterygoid 16U	Masseter (3×8–10U), temporalis (3×8U), lateral pterygoid (8U), and medial pterygoid (8U)	VAS (pain) Therabite® ruler (mand movements)	Sg better pain relief and movements in BoNT vs two other groups	MMFP	Sg results were more evident in "localized refractory MMFP" than referred types. Lasted 6 m No AE

(continued)

Table 16.1 (continued)

Author/ year	Study type	Patients	BoNT	Dose	Injection	Assessment	Outcome	Diagnosis	Comments
De la Torre Canales et al. 2020 [22]	Randomized, controlled clinical trial	$N = 100$ (20×3); oral appliance, Plc, low-, medium-, high-BoNT	Botox	Low: 80U; Medium: 140U; High: 200U 5 injections/ muscle, 5 mm apart	Low: 2 masseter (60U)+2 temporalis (20U), Medium: 2 masseter (100U)+2 temporalis (40U), High: 2 masseter (150U)+2 temporalis (50U)	VAS, PPT, EMG, MP, UI, CBCT	BoNT-A was more effective than Plc throughout 6 m and as effective as oral appliance over 24 w, regardless of the dose	MFP[a]	AE: reduced muscle activity and thickness + bone volume in high doses AE were dose-dependent and transient in low-doses
de Lima et al. 2021 [18]	Prospective, longitudinal	$N = 15$[b]	Botox	80U	Symmetrically in 4 points of each masseter and each temporalis, 20U/muscle	VAS (pain)	-Sg lower pain on day 15 vs baseline -Baseline values returned on day 30	TMD	Low-dose BoNT was effective, but short-lived No AE

Chaurand et al. 2021 [33]	Clinical trial	$N = 22$	Xeomin	100IU	15IU/trigger point in temporalis	VAS (pain), SF36	Sg pain relief: baseline vs 2 m; Sg QoL only at 2 m	Bilateral MFP + ≥4 trigger points/side and no joint issues	At 7 m, VAS and QoL inclined toward baseline No AE
Yoshida 2021 [34]	Clinical	$N = 53$	Botox	50–100U	Under EMG guidance, masseter, temporalis, medial/lateral pterygoid, posterior belly of digastric, and sternocleidomastoid with 3–6 m intervals depending on patient satisfaction	VAS	The mean improvement (0–100%), at the endpoint was 80.8% for MFP	TMD, no arthrogenous pathology	Minimum AE

AE adverse events, *BoNT* botulinum neurotoxin, *CBCT* cone-beam computed tomography, *d* day, *EMG* electromyography, *m* month, *MMFP* masticatory myofascial pain, *MP* masticatory performance, *NSg* nonsignificant, *OHIP-14* Oral Health Impact Profile questionnaire, *Plc* placebo, *PPT* pressure pain threshold, *QoL* quality of life, *SF36* short form (36), *Sg* significant, *TMD* temporomandibular disorder, *TMJ-QoL* temporomandibular joint replacement quality of life questionnaire, *TMJD* temporomandibular joint disorder, *UI* ultrasound imaging, *VAS* visual analog scale, *vs* versus *w* week

[a] Included subjects demonstrated myofascial pain ($N = 53$), myofascial pain/arthralgia ($N = 12$), myofascial pain/disc displacement with reduction ($N = 27$), and myofascial pain/disc displacement without reduction ($N = 8$)

[b] A total of 35 patients were evaluated in this study, 15 of whom had TMD

One of the reasons for the variability in BoNT application is that muscle size could impact the neuromuscular effect of BoNT. Therefore, bulkier and larger muscles would need more toxin to demonstrate the desired effects, and considering that muscle size is extremely variable among patients, the dosage of BoNT is adjusted on an "as needed" basis [36]. In addition, some studies modify the dosage according to the level of patient's complaint and symptoms [18, 34]. De la Torre Canales et al. [22] showed superior pain-controlling effects of BoNT-A compared to saline, regardless of its dosage. Considering that adverse events increase in patients who receive higher doses of the toxin, they suggested using the lowest possible dose, which would offer the same effect as higher dilutions. Relief seemed to be achieved through effects of both dose-dependent motor activity and antinociceptive effects of BoNT-A.

Another interesting observation among the evaluated studies was that BoNT had a better impact on patients with localized myalgia than those who suffered from referred myofascial pain. In individuals with this kind of pain, soreness extends to areas distant from the limits of the affected muscle (DC/TMD) [30, 32].

BoNT Injection for TMD Pain Primarily Attributed to Temporomandibular Joint Origin

TMD pain with arthrogenic origin has also been managed by BoNT-A (Table 16.2). In a clinical study, significant improvement was observed after bilateral injection of 300 U and 200 U Dysport into the masseter and temporalis muscles, respectively, of 13 patients with pain due to disc disorder and degenerative joint disease [37]. Thomas and Aronovich [38] injected 53 subjects with TMJ arthralgia and refractory arthrogenous and myogenous pain with placebo or Botox before arthroscopy and found better pain relief in those who had received BoNT-A. In a prospective cohort study [39], intraoral versus extraoral approach for electromyography (EMG)-guided BoNT-A injection into the lateral pterygoid muscle was tested in 20 joints of patients with anterior disc displacement with reduction. For extraoral injections, insertion was through the space formed by the zygomatic arch and the mandibular sigmoid notch below the center of the zygomatic arch in patients with closed mouths. The intraoral insertion point was above the upper molars, parallel to the occlusal plane and lateral to the maxillary tuberosity. Pain reduction was significant compared to baseline in both groups, but the intraoral approach took significantly less time and was better tolerated by the patients. As stated above, de la Torre Canales et al. [22] included 12 and 35 patients with arthralgia and disc displacement (± reduction) in their randomized clinical trial of 100 TMD cases and reported favorable results of BoNT-A injection into the temporalis and masseter muscles, even in low doses.

Another method for pain control in arthrogenic TMD is through intra-articular administration of BoNT. Animal studies have demonstrated that injection of Botox into rat TMJs can prevent neuropeptide release leading to decreases in persistent hypernociception related to albumin-induced arthritis [40]. Batifol et al. [20] conducted a retrospective study on 77 patients with severe chronic TMJ pain who had not responded to any treatments including intramuscular BoNT and intra-articular

Table 16.2 Summary of studies on the use of botulinum neurotoxin in temporomandibular joint-related pain management

Author/ year	Study type	Patients	BoNT	Dose	Injection	Assessment	Outcome	Diagnosis	Comments
Kim et al. 2016 [37]	Clinical study	N = 13[a]	Dysport® (aboA)	500U	Masseters (2 × 150U) +temporalis (2 × 100U) in three sites, 1cm apart	Pain intensity, disability points, chronic pain grade, depression index, grade of nonspecific physical symptoms	Sg pain relief pre- vs post-treatment	Disc disorders, degenerative joint diseases, osteoarthritis, and osteoarthrosis	
Thomas and Aronovich 2017 [38]	Retrospective cohort	N = 52 BoNT:30, Control: 22	Botox	≤50U/each masseter, ≤25U/each temporalis	Based on tenderness, 5, 10, or 15U were injected	MRI, VAS	Sg greater decrease of pain in BoNT vs control	Refractory MFP with arthrogenous and myogenous pain	BoNT was evaluated as an adjunct to arthroscopy
Batifol et al. 2018 [20]	Retrospective	N = 77	Botox	30U/joint	Posterior-superior condylar border in the joint space	VAS (pain), mouth opening, SF36	Sg pain relief baseline vs. 15 d, 1 m and 3 m, NSg changes in mouth opening Improved QoL	Severe, chronic, refractory TMJ pain, nonresponsive to all treatments	Intra-articular BoNT is not effective for mouth opening Transient AE
Altaweel 2019 [39]	Prospective cohort study	N = 20 joints Intraoral: 10 Extraoral: 10	Botox	20IU/ muscle	EMG guidance for LPM injection by intra- or extra-oral approach	MRI (clinical Dx) VAS (pain) EMG (LPM activity)	Sg pain relief in both groups vs baseline Sg tolerability in intra>extra Sg larger mean time in extra vs intra	ADDWR	Pain relief from 4th week lasting to 24th week in both groups

ADDWR anterior disc displacement with reduction, *AE* adverse events, *BoNT* botulinum neurotoxin, *Dx* diagnosis, *EMG* electromyography, *LPM* lateral pterygoid muscle, *MFP* myofascial pain, *MRI* magnetic resonance imaging, *NSg* nonsignificant, *Plc* placebo, *QoL* quality of life, *Sg* significant, *TMJ* temporomandibular joint, *VAS* visual analog scale, *vs* versus, *w* week

[a] Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) was used for the diagnosis of 21 TMDs, who were further classified by the Japanese Society for the Temporomandibular Joint criteria, after which there were five patients with disc disorder and eight with degenerative joint diseases, osteoarthritis, and osteoarthrosis, some may or may not have had parafunctional habits

sodium hyaluronate injections in the past 4 months. In an aseptic room, 30 U of Botox was injected into the joints following subcutaneous anesthesia. Doses of 20 U, 30 U, and 50 U were previously tested by the investigators, and 30 U was found to be optimal. Clinical significance was set at a two-point reduction of pain on visual analog scale (VAS), which was observed in 66% of the patients at 1 month, lasting up to the 3rd month post-injection. Improvements in mouth opening and quality of life were also noted.

Comment

BoNT-A has shown positive effects in reducing pain and discomfort of TMD patients, and its tolerability and minimal adverse events (especially in low doses) make it suitable for treatment of this disorder. Based on AAN criteria, BoNT-A is *"probably effective"* for the treatment of pain in TMD. Double-blind, placebo-controlled, class I clinical trials with extended follow-up periods may provide further evidence to establish the use of BoNT as *"effective."*

Considering the multifactorial nature of TMD pain, the first step in rendering a treatment plan would be to reach a diagnosis and attempt to identify its major attributable source(s), that is, myogenous or arthrogenous. For intramuscular injections, it is best to consider the bulk and size of the muscle and to use the lowest dose possible with 30 day recalls to evaluate the possibility of further rounds of treatment. Planning should be individualized for each patient while contemplating additional treatment options in those affected by referred myofascial pain. Considering the lack of information on intra-articular injections, they should be saved as a last resort and only if the operator has the necessary skills to perform a safe injection.

Bruxism

Definition, Classification, and Epidemiology

Bruxism, generally classified as sleep and awake subtypes, is an oral movement disorder encompassing a range of facial muscle activities of various causes and clinical relevance. In 2013, a multidisciplinary group of experts gathered to form a consensus on its definition and diagnostic criteria [41], which was later updated in 2018 [42]. Sleep and awake bruxism were respectively described as "masticatory muscle activities that occur during sleep (characterized as rhythmic or nonrhythmic) and wakefulness (characterized by repetitive or sustained tooth contact and/or by bracing or thrusting of the mandible)" in otherwise healthy individuals. Clenching was considered as "teeth touching not for swallowing purposes" and bracing/thrusting as "increased levels of masticatory muscle activity without tooth contacts" [42]. Sleep bruxism has been reported to occur in 7.4% of the population, and the prevalence of awake bruxism is recorded as 22.1–31% [10]. However, their true incidence remains unknown [35].

Bruxism may be harmless and have one or more negative consequences or even be a protective behavior [42]. It is clear that treatments are directed toward the second situation in which bruxism is a risk factor for inducing harmful events like orofacial pain.

Assessment of bruxism includes noninstrumental and instrumental approaches. Examples of the former are questionnaires, oral reports, and clinical examination. The latter consists of EMG recordings and polysomnography ideally coupled with audio/video recordings. Due to the multifactorial nature of the disorder, a reliable cutoff for types that pose as a risk factor is not practical [42, 43]. Both types of bruxism are graded as *possible*, *probable*, and *definite* according to (1) self-report only (minimum recording of one or 2 weeks), (2) clinical examination±self-report, and (3) instrumental determination±self-report±clinical examination, respectively [42].

Management of Bruxism

Clinical consequences of bruxism include occlusal wear, tooth damage, implant complications, and muscle or joint pain, but there is no agreement on which of them necessitate treatment of the behavior [35, 42, 43]. Both types of bruxism have shown correlation with TMD pain [44], but the possibility that they are a direct cause of TMD pain has not been conclusively established [45], and their amount and intensity do not necessarily result in increased muscle overloading and more pain [35, 46]. The need for interventions appears to be related to the extent of behavior-related harm detected by the physician and the patient's complaint. Pharmacotherapy (e.g., tricyclic antidepressant, protein pump inhibitors, BoNT injections); electromyography, biofeedback, and transcutaneous electrical neuromuscular stimulation; occlusal devices; muscle stretching; and combination approaches have been used with inconsistent results and questionable long-term effectiveness [10, 35].

Efficacy of BoNT in the Treatment of Pain Associated with Bruxism

The first report of BoNT injection for the treatment of bruxism was in 1990 [47]. A 32-year-old woman who had developed bruxism while recovering from a coma following a car accident 6 month earlier was injected with 25 U of toxin-hemagglutinin complex of botulinum toxin into both temporal and masseter muscles after partial recovery from her coma. A significant decrease in her bruxism was observed which lasted for 8 weeks with no effect on or interference with patient's feeding [47].

The most important aspect of bruxism that leads to clinical consequences necessitating treatment is "masticatory muscle activity" [42]. Therefore, a reasonable approach to its management would be to decrease the activity of masticatory muscles in a safe way, without compromising their physiological functions. BoNT enters nerve endings in the neuromuscular junctions, where it inhibits acetylcholine

release from synaptic terminals through cleaving SNAREs which results in reduced muscle contraction [10]. The effects are usually noticeable within a few days to 1 week. The highest point of efficacy occurs after five to six weeks, and gradual decrease is seen thereafter, returning to its pre-injection state, 12 weeks after injection [48]. In an animal study, 1 month after BoNT administration into the masseter of rabbits, a reduction in amplitude and duration of EMG was observed with concomitant histologic atrophy of muscle fibers and increased collagen. After 3 months, some innervation had occurred as demonstrated by normal EMG duration and slightly increased cell division and fiber regeneration. However, microscopically some deficits including hypertrophied/atrophied/dead fibers and fibrosis remained [49]. In addition to its paralyzing effect on the masticatory muscles, BoNT may also have an antinociceptive effect in bruxism cases associated with pain (see Management of Temporomandibular Disorders above).

An interesting speculation regarding BoNT application in bruxism was that the feedback loop of the trigeminal motor nucleus might be affected by toxin-provoked muscle paralysis leading to suppression of the "central bruxism generator" [50]. Similarly, it was proposed that the peripheral effect of BoNT may have a central diminishing consequence, either directly or by decreasing central input following reduction of peripheral activity [48]. The central and autonomic nervous systems have been suggested to have a role in generating phasic or tonic (rhythmic or non-rhythmic) masticatory muscle activity during sleep. It has been hypothesized that brain chemicals may control sleep-associated events and airway patency during sleep and enhance rhythmic masticatory muscle activity (RMMA) that occurs prior to sleep bruxism (SB) episodes [51].

Based on recent studies on BoNT-A administered to bruxers with pain (Table 16.3) [18, 50, 52–57], it seems that this toxin as a minimum can reduce bruxism-associated pain.

The literature (Medline and Google Scholar search) includes two class II studies [53, 54] and one class 1 trial [50] that have shown significant decrease in pain, providing level B evidence indicating BoNT to be "*probably effective*" for pain management in bruxers. Almost all studies used onabotulinumtoxinA (Botox), which was injected into the masseter (40–48 U) or masseter+temporalis (80–100 U) muscles into 3–4 points. Effects were reported as soon as 12 days post-injection [52], and minimum return to baseline values was 90 days [18], while significantly less pain was reported even at 24 weeks in patients injected with BoNT compared to saline [50]. Most of the studies evaluated SB and used questionnaires/self-reports and examination. In comparison between BoNT and occlusal splints in a randomized single-blind prospective trial on 73 patients, Yurttutan et al. [53] reported significant decrease of pain by both approaches; however, patients receiving BoNT and BoNT+occlusal splint had significantly less pain compared to those with occlusal splints only, while no differences were found between the BoNT groups. They suggested no added benefit of occlusal splints, especially considering the difficulties in their application and the need for long-term compliance due to their relatively late-onset effects. BoNT was ultimately proposed as an effective treatment for bruxism-related pain with limited need for commitment and long-term results. Kaya and

Table 16.3 Recent studies using botulinum toxin to manage orofacial pain in patients with sleep and/or awake bruxism

Author/ year	Study type	Patients	BoNT	Diagnosis	Dose	Injection	Assessment	Outcome	Comments
Asutay et al. 2017 [52]	Retrospective data analysis	*N* = 25	Botox	SB (clinical)	40 MU	Origin, insertion, ant, and post masseter (5 MU/site)	VAS, 0, 2 w, 1 m, 3 m, 4 m, 6 m	Sg pain reduction except between 2 w vs 4 m and 1 m vs 3 m; Max mouth opening: no changes	Mean effect onset: 12 d Mean loss of effect: 4.8 m No AE
Jadhao et al. 2017 [57]	Double-blind, placebo controlled, randomized clinical trial	*N* = 24 Saline: 8 BoNT: 8 None: 8	Botox	SB (self-report, examination)	100U	Masseters (30U/side) and temporalis (20U/ muscle, in 3 points)	VAS (pain at rest and chewing), and occlusal force analysis 0. 1 w, 3 m, 6 m	VAS decreased only in BoNT group Sg decrease in occlusal force in BoNT vs saline and control	Lowest level of occlusal force was in 3rd m after BoNT
Al-Wayli 2017 [55]	Randomized controlled parallel group clinical trial	*N*=50 BoNT: 25 Other treatments: 25	Botox	"Probable" SB[a] with bilateral masseter pain	40U	Masseter (20U/side in 3 points)	VAS, 3 w, 2 m, 6 m, 1 y	Sg decrease in mean pain score in BoNT vs conventional group at all time points No improvement in conventional treatment	Suggestion: evaluation 15 d after injection and control after 3–4 m for repeat if necessary
Ondo et al. 2018 [54]	Randomized double-blind, placebo-controlled followed by open-label	*N* = 22 Saline: 9 BoNT: 13	Botox	SB (questionnaires, examination, PSG using ICSD-3 criteria)	200U	Masseters (60U/ muscle in 2 points) and temporalis (40U/ muscle, in 3 points)	1st efficacy endpoint: CGI, 2nd endpoint: VAS of change in bruxism and pain 4–8 w after injection	CGI and VAS of change, both Sg favored BoNT	Two BoNT patients reported cosmetic smile change

(continued)

Table 16.3 (continued)

Author/ year	Study type	Patients	BoNT	Diagnosis	Dose	Injection	Assessment	Outcome	Comments
Yurttutan et al. 2019 [53]	Randomized, single-blinded, prospective	*N* = 73 OS: 25 BoNT: 24 BoNT+OS: 24	Botox	Myofascial pain due to bruxism (RDC/TMD, questionnaire)	90U	2 masseters (5 × 6U in each); 2 temporalis (3 × 5U in each)	TMD-PS, GCPS, OBC, JFLS, and VAS (muscle palpation), 0 and 6 m	Sg VAS decrease in all groups Sg VAS decrease in both BoNT groups vs OS-only group, but not between BoNT groups	One patient excluded for asymmetric smiling
de Lima et al. 2021 [18]	Prospective, longitudinal	*N* = 20[b] SB: 12 AB: 8	Botox	Pain (DC/TMD) due to SB and AB (self-reports, clinical exams using ICSD)	80U	Symmetrically in 4 points of each masseter and each temporalis, 20U/ muscle	VAS (pain), 0, 15, 30, 60, 90, 180 d	-Sg lower pain on day 15 vs baseline -Baseline values returned on day 90	No AE
Kaya and Ataoglu 2021 [56]	Prospective, randomized, clinical trial	*N* = 40 OS: 20 BoNT: 20	Botulinum toxin type A	Myofascial pain due to bruxism (referred patients, examination)	48U	Masseter: 24U/side, 8U/point	VAS (pain), modular system (max BF), 0, 2 w, 6 w, 3 m, 6 m	VAS reduction in both groups, no Sg difference In BoNT, BF decreased in 2nd and 6th weeks, but was not different in 3rd and 6th months vs day 0 In OS, BF only increased in 6 m	

M Alwayli et al. 2021 [50]	Prospective, double-blind, randomized	*N* = 40 Saline: 20 BoNT: 20	Botox	"Probable" sleep/awake bruxism[a]	40U	Masseters (20U/side, 5U in 4 points)	VPS (pain at rest and chewing) 0, 2, 4, 8, 12, 16, 18, and 24 w	Sg decrease in VPS after 2 w in BoNT Mean difference of VPS increased from 8–24 w in BoNT Sg less pain at 2, 8, and 24 w in BoNT vs saline	No AE

AASM American Academy of Sleep Medicine, *AB* awake bruxism, *AE* adverse events, *ant* anterior, *BF* bite force, *BoNT* botulinum neurotoxin, *CGI* clinical global impression, *d* day, *DC/TMD* Diagnostic Criteria for Temporomandibular Disorders, *EMG* electromyography, *GCPS* Graded Chronic Pain Scale: *IAF* Fonseca anamnestic index, *ICSD* International Classification of Sleep Disorders, *JFLS* Jaw Function Limitation Scale, *Max* maximum, *m* month, *OBC* Oral Behavior Checklist, *OS* occlusal splint, *PSG* polysomnography, *post* posterior, *RDC/TMD* Research Diagnostic Criteria for Temporomandibular Disorders, *RMMA* rhythmic masticatory muscle activity, *SB* sleep bruxism, *Sg* significant, *TMD-PS* Temporomandibular Disorder Pain Screener, *VAS* visual analog scale, *VPS* visual pain scale, *y* year

[a]Based on 2013 consensus criteria (reference 40)

[b]A total of 35 patients were evaluated in this study, 15 of which had TMD with no bruxism, detailed in Table 16.1

wAtaoglu [56] also compared these methods in 40 patients and found no difference in the reduction of pain between the two groups. In contrast to Yurttutan et al. [53], who administered BoNT to both masseter and temporalis muscles, they only injected the masseters and did not include a BoNT+occlusal splint group. Nonetheless, they proposed using BoNT in patients who cannot use occlusal splints. It has been suggested that BoNT injection may be even more useful in bruxers with clinical consequences other than pain, since their cooperation to use occlusal splints may be even less, due to the lack of a strong incentive like pain [48].

Notwithstanding the foregoing, it has been indicated that the effect of BoNT may be mainly subjective and it may not have a major impact on reducing the actual number of episodes and the genesis of RMMA and bruxism [58, 59]. The perceived effect by the patient is probably due to the lowering in masseter intensity as evidenced by EMG data [58]. Further controlled studies objectively measuring outcomes like muscle forces, sleep variables, and bruxism events have been proposed [48, 59].

Comment

Based on several high-quality studies in the literature and using the AAN criteria, BoNT-A is *"probably effective"* for the management of patients with bruxism-related pain, successfully providing them with relief. BoNT can be applied as a substitute for occlusal splints, which require high maintenance and can be uncomfortable, in addition to demonstrating late-onset effects. This toxin can even be prescribed to bruxers that have clinical consequences other than pain. Larger class I trials with longer follow-up on bruxers with pain are required to provide level A evidence for the application of BoNT in controlling pain in individuals with bruxism.

Neuropathic Orofacial Pain

By definition, neuropathic pain refers to allodynia, hyperalgesia, and/or numbness of the skin, viscera, and musculoskeletal system directly caused by a disease/injury to nerves or structures of the CNS. It may be similar to pain felt during inflammation, but the distinction is that it must involve neural tissues. Its prevalence has been estimated at 6.9–10% of the population and is described as burning, sharp, or electric [1, 5, 7].

Neuropathic OFP is a blanket term used to cover painful lesions/diseases of the cranial nerves [1, 5]. ICOP has used the term "orofacial pain attributed to lesion or disease of the cranial nerves" and divided the clinical entities that fall under this category into those related to the trigeminal, or the glossopharyngeal nerves.

Pain Attributed to Lesions or Diseases of the Glossopharyngeal Nerve

Glossopharyngeal Neuralgia (GN)

Definition, Classification, and Epidemiology

GN is described as sudden, short, unilateral, shock-like, or stabbing severe pain lasting from a few seconds to 2 min in the area innervated by the glossopharyngeal and the auricular and pharyngeal branches of the vagus nerve, which is felt in the ear, tongue base, tonsillar fossa, and the mandibular angle, incited by jaw movements like swallowing, talking, and coughing. The classic type is diagnosed by MRI or during surgery, while secondary GN is characterized by an underlying disease causing neuralgia. It is extremely rare, affecting approximately 0.2–0.8/100,000 individuals per year, mostly men over 50 years of age [7, 9, 60].

Management of Glossopharyngeal Neuralgia

Pharmacotherapy including agents like carbamazepine, gabapentin, and pregabalin is the first line of treatment in GN management and could be supplemented with a glossopharyngeal nerve block, which has demonstrated favorable results. Surgical intervention is preserved for cases not responding to these options [60].

Efficacy of BoNT in the Treatment of Glossopharyngeal Neuralgia

We only found one publication on BoNT application in GN, which reported that neither Dysport nor Botox show any effect on pain control [61].

Comments

Until further studies on the efficacy of BoNT on GN are conducted, we cannot comment on its efficacy in reducing pain intensity in these patients. The only study in this regard did not show a positive effect of BoNT.

Pain Attributed to Lesions or Diseases of the Trigeminal Nerve

Trigeminal Neuralgia (TN)

Definition, Classification, and Epidemiology

According to ICOP, TN is characterized by recurring, unilateral, short, electric, shock-like pains, precipitated by innocuous stimuli that appear and cease suddenly and are limited to the distribution of one or more divisions of the trigeminal nerve. The pain is of severe intensity, and the attacks last from a fraction of a second up to 2 min. They occur inside the trigeminal dermatome with no radiation [9].

Its subtypes include classical or primary, secondary (due to multiple sclerosis, space-occupying lesion, other causes), and idiopathic [9]. According to the European Academy of Neurology (EAN), the difference between classical and idiopathic is that classical occurs as a result of "neurovascular compression with morphological changes of the trigeminal root," while idiopathic has "no neurovascular contact (NVC) or NVC without morphological changes of the trigeminal root" [62]. For diagnosis, close collaboration between neurologists, neuroradiologists, and dentists using MRI with or without diffusion tensor imaging, brain gray matter analysis, and trigeminal reflexes is recommended [62, 63]. The symptomatology is basically the same in all three subtypes [63].

TN occurs more commonly in women, rarely before 40 years of age, with an incidence that ranges between 0.03% and 0.3% in the general population, with higher incidence rates reported in the United Kingdom (27/100,000/year) compared to the United States (4/100,000/year) [64].

Management of Trigeminal Neuralgia

Pharmacological treatment is the first line of therapy for long-term TN pain, which includes carbamazepine, oxcarbazepine, and other anticonvulsant drugs. In addition to ¼–½ of patients becoming refractory to pharmacotherapy, there are a number of side effects associated with these drugs. Surgical options like microvascular decompression, gamma-knife surgery, and neuro-ablative therapy are offered after the failure of medical treatments. While their possibility should be mentioned in the early stages of treatment, the patient should also be made aware of their potential to cause side effects. Another safer and more acceptable therapy is BoNT-A injection, which is included in the 2019 guideline of the EAN on trigeminal neuralgia, to be used as add-on therapy for medium-term management. This is an important addition considering the high rate of persistent symptoms or side effects following application of carbamazepine and oxcarbazepine [10, 62, 63, 65].

Efficacy of BoNT in the Treatment of Trigeminal Neuralgia

The exact mechanism by which BoNT controls TN pain is uncertain. Both central and local/trigeminal antinociceptive effects have been suggested. Studies show that the antinociceptive activity of BoNT following its peripheral administration is due to a decrease in central sensitization and suppression of overexpression of nociceptors [66]. Additionally, the axonal transport of this toxin to the CNS can also contribute to its analgesic effects [10].

Matak et al. [67] evaluated the central antinociceptive function of BoNT-A in a formalin-induced model of facial pain. Their study included injection of low doses of toxin into the whisker pad and sensory trigeminal ganglion of rats. Colchicine was used as an inhibitor. They showed that trigeminal sensory neurons are responsible for axonal BoNT transport which is a requisite for its antinociceptive effects, even when directly administered to the ganglion. The conclusion was that the sensory root is the path by which BoNT-A is transmitted to the trigeminal nociceptive

projections in the CNS. Similarly, in a rat TN model based on chronic constriction injury of the infraorbital nerve, the antinociceptive effect of peripherally administered BoNT-A was attributed to its direct action on the trigeminal nucleus through axonal transport. The expression of some of the TRP family members (nonselective cation channel proteins) was downregulated, and central sensitization was decreased [68]. A recent animal study on rats indicated that injection of BoNT-A into the orofacial area reduces pain via axonal and hematogenous transport. Using a chemotherapy-induced bilateral neuropathic pain model, the authors showed that following unilateral peripheral administration of BoNT-A, the head withdrawal threshold was enhanced bilaterally. They also used an infraorbital nerve constriction model to demonstrate intensified head withdrawal threshold after peripheral toxin injection in the contralateral side. Another interesting observation was that intradermal injections resulted in the appearance of BoNT-A in the circulation. Finally, they reported identifying the C-terminal half of the heavy chain of BoNT-A in the neurons of both right and left trigeminal ganglia following unilateral peripheral injection [69]. Further studies are required to elucidate the exact mechanisms involved in the antinociceptive effects of BoNT.

Based on recent systematic reviews and meta-analyses, current evidence suggests that BoNT-A application in TN is an effective and safe option for reducing pain intensity and frequency with minimal transient side effects [70–73]. However, high-quality studies providing high level of evidence for its widespread usage in this disease are still lacking [36, 70–74]. Since the last edition of this book with one reported class I trial on TN [75], 12 studies [65, 76–86] and several case reports [74] have been added to the literature, of which two are class I double-blind, randomized, placebo-controlled studies [76, 78] (Table 16.4), conferring Level A evidence for BoNT efficacy in TN treatment. There are still no guidelines providing definitive specifications for dosage, injection site, number of injections, administration route or number, and time of repeats.

Dosage and number of injection sites has ranged from 15 IU [83] to 200 U [65] and 1 [84, 86] to 25 points [77, 81, 85], respectively. The lowest dose reported in the literature seems to be from an open-label trial on 13 patients, which found 6.45–9.11 U to be effective, depending upon the pain distribution area [87]. Short-term efficacy has been reported to be similar between higher (75 U) and lower doses (25 U) of BoNT [78]. Comparable effectiveness of small and large doses has also been confirmed in other studies [65, 77]. In addition to dosage, it is interesting that repetition of injections also did not affect therapy results. Neither treatment outcome nor side effects were different in single versus repeated injections, and adverse events were suggested to be more closely associated with the injection method [81].

The administration route has been mostly intradermal, or intra mucosal in trigger points (if identifiable) or along the distribution of the affected nerve and usually involves multiple points [77–79, 81–83, 85]. An open-label trial used a different approach that included only one or two injections by which BoNT was administered into the maxillary and/or mandibular nerve roots near the ganglion. The maxillary root was targeted through the upper edge of the zygomatic arch between the orbital rim and ear, while the middle of the lower edge of the zygomatic arch was the

Table 16.4 Overview of studies[a] using botulinum neurotoxin in the management of trigeminal neuralgia

Author/year	Study type	Patients	BoNT	Dosage	Injection	Assessment	Outcome	TN	Comments
Zúñiga et al. 2013 [76]	Double-blind, randomized, placebo-controlled	*N* = 36; BoNT: 20 Plc: 16	Botox (onaA)	50U	Subcutaneous; 1cm apart, along branch(es) + 10U in masseter for V3 involvement	VAS (pain), functional impact score, paroxysm (N), SF36	Sg decrease at 3 m in pain and paroxysm No Sg change in functional impact and SF36	Essential IASP, 1994	Synergistic effect of BoNT with other meds was reported
Li et al. 2014 [77]	Open-label	*N* = 88	HengLi® Lanzhou	25–170U	Intradermal &/or intramucosal in trigger points; 15 mm apart (total, 15–25 points with 2.5–5 IU/point, less for gum)	VAS (pain extent), attack frequency and side effects, PGIC	Effectiveness was 100% at 2 m and decreased to 38.6% at 14 m	One-branch classical	Effectiveness: percentage of patients with ≥50% reduction in VAS. Mild and transient AE
Zhang et al. 2014 [78]	Double-blind, randomized, placebo-controlled, parallel group	*N* = 84, BoNT 75U: 29, 25U: 27 Plc: 28	Lanzhou	25U or 75U	Intradermal and/or submucosal, at pain site; 20 points with 0.05 ml/site	VAS (pain severity), PGIC, AE, attack frequency	Sg improved VAS, PGIC, and efficacy in both BoNTs vs Plc No Sg changes between 25U vs 75U	Classical ICHD-II	Effectiveness: patients with ≥50% reduction in VAS. Mild-moderate and transient AE gone in 6 w
Xia et al. 2016 [79]	Open-label	*N* = 87	HengLi® Lanzhou	NS	Intracutaneous in trigger points or in pain distribution area: 15 mm apart (total, 15–20 sites)	VAS, side effects, SF-36, and sleep interference-, HAMA-, and HAMD-scores at 1, 2, 4, and 8 w	Sg improved VAS (all times) Sg improved efficacy at 1 w vs 2 w Sg improved anxiety and depression Sg improved sleep (all times) Sg improved QoL at 8 w[b]	TN	Effectiveness: patients with VAS reduction rate ≥50% Mild AE gone in 6 w

Türk Börü et al. 2017 [80]	Open-label	N = 27	Botox	50U for each root	Maxillary and/or mandibular roots; repeated if required	VAS (pain severity), attack frequency (N/d) and PGIC	Sg improved VAS and attack frequency at 1 w, 2 m, 6 m Effective response (88.9%) at 6 m -PGIC: 85.1% improved "very much" or "much"	Classical ICHD-2	Effectiveness: ≥50% VAS decrease from baseline to 6 m Transient facial weakness (N = 1); permanent masseter weakness (N = 2)
Zhang et al. 2017 [81]	Open-label	N = 81; Single dose: 44 Repeated dose: 37	Lanzhou, China	Single dose: 70–100U; Repeated dose: 50–70U, exactly repeated after 2 w	Intradermal and/or intramucosal at pain site; multiple: 15 mm apart (total, 15–25 sites with 1.25–5 U/site)	VAS (pain), attack frequency, time between treatment and effect, time to peak effect, and AE	No Sg difference in all factors at 6 m between single and repeated doses Sg longer duration of efficacy in single dose	Classical ICHD-2	Mild-moderate AE
Gorimanipalli et al. 2017 [82]	Retrospective observational	N = 23	Botox	Total of 54 injections in all 23 patients	Intradermal or submucosal in trigger points or pain distribution area: 3IU/cm^2 of pain area	VAS (pain intensity), days to onset of relief, weeks of relief	Sg improved VAS at 3 m 100% response; Mean duration of maximum relief: 26 w	Classical ICHD-2	Response: >50% pain relief -Only minor AE
Liu et al. 2018 [65]	Open-label	N = 43; ≥80 y: 14, <60 y: 29	Lanzhou, China	45–150U in older and 30–200U in younger	Intradermal and/or intramucosal in trigger zones	VAS (pain severity)	Sg lower VAS at 1 m than at baseline in both groups	Classic idiopathic ICHD-II	Mild-moderate AE, gone in 3 w

(continued)

Table 16.4 (continued)

Author/year	Study type	Patients	BoNT	Dosage	Injection	Assessment	Outcome	TN	Comments
Caldera et al. 2018 [83]	Observational	$N = 22$	BTX-A	15–50IU	Directly in trigger point or intradermal in pain distribution area	VAS (pain) at 10, 20, 30, 60, and 90 d	Sg improved VAS at all times No Sg difference between high vs low doses No Sg difference between trigger point vs pain distribution area	TN ICHD-II	BoNT was given as adjunct to medical therapy Maximum response: at day 60 post-BoNT No serious AE
Crespi et al. 2019 [84]	Prospective, open-label	$N = 10$ (one excluded for efficacy outcomes)	BoNT-A	25IU	Percutaneous navigation-assisted toward SPG	NRS (attack intensity), AE, PGIC, N of attacks, and function level at 0 and 5–8 w	Sg improvement in NRS and % of the day with persistent pain: No Sg improvement in attack N	Refractory classical ICHD-3b	Main efficacy endpoint: ≥50% reduction in median attack N/days between baseline and 5–8 w AE gone in 1 m
Zhang et al/2019 [85]	Follow-up retrospective study	$N = 152$	HengLi® Lanzhou	Low dose: <40U, Medium dose: 40–70U, High dose: >70U	Intradermal and/or intramucosal in trigger points; multiple: 15–20 mm apart (total, 15–25 sites with 1.25–5 U/site). Repeated if not improved after 2 w	VAS (pain extent), AE	Overall effective rate: 89.4%; Disease course and branch N, but not injection N affected incidence of side effects	Classical ICHD-2	Overall effective rate: % of patients with reduction by ≥50% Effective for 28 m suggests long-term control Clinical response may be patient-specific

Yoshida/2020 [86]	Open-label	$N = 10$	Botox	50U	SPG with CAD/CAM-derived injection guide	VAS (pain severity) & frequency at 0, 2 w, 4 w, 8 w, and 12 w	Sg improved VAS and pain frequency between baseline and endpoint All patients responded	Classical ICHD-3b	Responders: ≥50% reduction in VAS and pain frequency from baseline to endpoint No AE

AE adverse events, *BoNT* botulinum neurotoxin, *d* day, *HAMA* Hamilton Anxiety Scale, *HAMD* Hamilton Depression Scale, *ICHD* International Classification of Headache Disorders, *m* month, *NRS* numeric rating scale, *NS* not specified, *PGIC* Patients Global Impression of Change, *Plc* placebo, *QoL* quality of life, *SF36* short form (36), *Sg* significant, *SPG* sphenopalatine ganglion, *VAS* visual analog scale, *w* week

[a]Since the previous edition

[b]Except for physical function

insertion point for the mandibular root with predefined depths and needle rotations. The treatment was well tolerated, and 88.9% of the patients showed ≥50% reduction in pain in the 6th month, and 2 out of 17 patients were recurrence-free for 2 years [80]. This technique does not require a radioscopic or echographic guide but depends on the operator's skill.

Another injection option is the administration of BoNT toward the sphenopalatine ganglion. This method has been applied using a navigation device (MultiGuide®, aided by surgical navigation) [84] and a CAD/CAM-derived injection guide [86] on ten patients in each study. The latter study achieved response by all participants, whereas the former observed a significant reduction in attack intensity but not in its main efficacy endpoint, which was ≥50% reduction in median attack numbers per day.

Comments

Despite the "A" level of evidence for the effective use of BoNT in TN treatment [88], a guideline describing optimal doses, administration routes, number of injections, etc. is yet to be developed. To prevent side effects, tolerance, patient discomfort, and increased cost, it is recommended that the lowest dose with the smallest number of injections per site be used for TN management and injections be repeated only when pain returns and not at the perceived endpoint of BoNT efficacy. According to existing data, 25–40 U BoNT administered intra-dermally/mucosally into 15–20 sites (2–2.5 U/point) is recommended for TN therapy [88]. Large well-designed, double-blind, placebo-controlled clinical trials with long follow-up periods are needed to determine the optimum treatment method and the efficacy, safety, and tolerability of the less used injection techniques. Pharmaceutical engineering to design target-specific BoNTs focusing on pain neurotransmission could be an interesting subject for future research.

Other Trigeminal Neuropathic Pains

In these types, the criteria of neuropathic pain are satisfied, and their major difference with TN is that the regions with allodynia are larger in the former compared to the punctate precipitation points of the latter.

Herpetic, Post-herpetic, Post-traumatic Trigeminal Neuropathic Pain and Other Disorders'

Definition, Classification, and Epidemiology

The herpetic and post-herpetic subtypes are recognized as pain on one side of the face in the area covering at least one of the trigeminal branches with a duration of more than 3 months and related to signs/symptoms of acute herpes zoster ("herpetic') in the same region as the pain or temporal relation to the acute infection

("post-herpetic"). Confirmation by PCR (virus in CSF or its DNA in the base of the eruption) or direct immunofluorescence assay (VZV antigen) of the original infection is required [9]. Post-herpetic neuralgia is more common in men and has an overall estimated incidence of 3.9–42.0/100,000 person per year, which increases with age. In the trigeminal region, it affects the ophthalmic nerve more often, but its specific incidence is not known and has been reported to be the second most common site of reactivation after the thoracic dorsal root ganglion [7, 9, 89, 90].

Post-traumatic trigeminal neuropathic pain (PTTNP) develops within 6 months after any kind of trauma to the peripheral trigeminal nerve(s) and leads to persisting or recurring pain in one or both sides of the face or oral cavity (>3 months), with or without other signs of nerve dysfunction. The pain should be accountable by detecting a lesion of the nerve(s) by acceptable diagnostic tests, and somatosensory symptoms may be positive or negative. Dental interventions constitute an important cause of injury and can be caused by injections, endodontic therapy, tooth extractions, and surgical procedures, including implant placement [9]. The incidence of this type of pain is extremely difficult to assess, since there is a large individual variability following similar injuries and different procedures have different odds of causing PTTNP, which have been reported to range from 0.3% to 13% [1, 91].

Management of Herpetic, Post-herpetic, Post-traumatic Trigeminal Neuropathic Pain and Other Disorders

Due to the lack of large studies with adequate treatment duration and follow-up periods, an exact management protocol for post-herpetic trigeminal neuropathic pain does not exist, and the evidence is generally insufficient. The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG) has recommended antidepressant, anticonvulsant, and anxiolytic medication as first line of therapy, 5% lidocaine and 8% capsaicin patches and tramadol as second-line therapy, and BoNT and opioids as third-line therapy [90].

For PTTNP, there is no consensus on the best timing and treatment modality, and most approaches have not rendered favorable results, especially considering the low drug response rate (11%) of PTTNP compared to other neuropathic pain entities (20–40%). Therefore, management of these patients mostly involves improving quality of life through coping strategies and minimizing pain and functional impairments [92, 93].

Efficacy of BoNT in the Treatment of Post-herpetic Trigeminal Neuralgia

BoNT administration can be a helpful option for the management of post-herpetic neuralgia, considering that the disorder arises more commonly in older people who have underlying comorbidities that limit certain strategies. According to Safarpour and Jabbari [88] and based on two AAN class I studies, there is Level A evidence for the efficacy of BoNT therapy in post-herpetic neuralgia. However, the information on the treatment outcome of this toxin in trigeminal nerve involvement is insufficient. The importance of this issue is that studies have shown that trigeminal

herpes could be more painful than involvement of other nerves [94] and has been known to respond less to treatments and be more difficult to manage [95, 96]. It has been suggested that trials on treatment strategies for post-herpetic neuralgia should analyze different locations, separately [97].

In a prospective, randomized, placebo-controlled, double-blind, parallel group study, 60 participants were allocated into placebo, lidocaine, and BoNT (BTX-A, Lanzhou, China) groups (20 patients per group). Subcutaneous injections of BTX-A were given 1–2 cm apart, and depending on the painful area, patients received up to 200 U of the toxin. Improvements in pain intensity (visual analogue scale, VAS), sleep time (hours), and the reduced need for opioid use were significantly greater in the BoNT group compared to each of the other groups. Post-herpetic neuralgia was located in the orofacial region in 11 of the patients, but no further information was provided on them, except that they experienced more pain during the injections [98].

Another study reported significant pain relief within 16 weeks in 19 post-herpetic pain patients following administration of 500 U BoNT (Dysport) in 25 points. Three of them had ophthalmic involvement, and the authors stated that pain reduction was not associated with "dermatomal involvement" [99].

In an observation of eight cases with intractable post-herpetic neuralgia, the trigeminal nerve was involved in six out of eight patients (V1 and V2). The thoracic region was the site of involvement in the other two cases. A total dose of 50–100 U BoNT (Botox) was injected intradermally at multiple sites 2 cm apart, which showed significant pain relief in five out of eight subjects, starting from day 7 and continuing to approximately 74 days post-injection. Further information on the involved nerve of the five patients who demonstrated pain relief was not provided [100].

Comments

It is not yet clear whether post-herpetic neuralgia originating from the trigeminal nerve responds differently to BoNT therapy as compared to other nerves involved by this disorder. The preliminary data demonstrates that BoNT-A relieves pain in some patients with recalcitrant post-herpetic pain in the trigeminal distribution. To elucidate this issue, further studies, preferably controlled clinical trials, are needed to determine whether there is a need to modify the existing BoNT injection technique for patients with post-herpetic trigeminal neuropathy.

Efficacy of BoNT in the Treatment of Post-traumatic Trigeminal Neuropathic Pain

There is Level A evidence, based on two AAN class I studies, confirming the effectiveness of BoNT treatment in post-traumatic neuralgia, none of which included PTTNP cases [88]. It has been suggested that PTTNP is more challenging to manage than other neuropathic pain disorders like spinal traumatic neuropathies, due to possible differences in pathophysiological mechanisms [101].

In order to gather and present data on BoNT effectiveness in post-traumatic neuralgia affecting the trigeminal nerve and the orofacial region, a literature search using Medline and Google Scholar showed significant variability in the descriptive nomenclature and considerable overlap in the classifications. "Atypical odontalgia" has been considered a subtype of persistent idiopathic facial pain (PIFP) by ICHD-3; however, at the same time, when associated with a history of trauma, the ICHD-3 states that it could also be classified as a subtype of PTTNP but declares insufficient data to suggest definitive diagnostic criteria. Furthermore, according to ICHD-3, "A continuum seems to exist from *Persistent idiopathic facial pain* induced by insignificant trauma to *Painful post-traumatic trigeminal neuropathy* caused obviously by a significant insult to the peripheral nerves" [102]. ICOP suggests diagnostic tests and other criteria that may be helpful to differentiate these disorders [9]. However, considering the limited number of reported cases in the literature in addition to different descriptive terms and inadequate information in the existing reports (especially those that are older), it was not possible to accurately differentiate between these two entities. Therefore, we have divided all studies on PTTNP, dentoalveolar neuropathic pain, atypical odontalgia, persistent idiopathic dental/facial neuralgia, and similar terms into two lagre groups: those that have a documented history of any kind of trauma and are suggestive of PTTNP (Table 16.5) and those with no evidence of any traumatic event that would be suggestive of persistent idiopathic facial/dentoalveolar pain (Table 16.6, also see sections "Persistent Idiopathic Facial Pain (PIFP)" and "Persistent Idiopathic Dentoalveolar Pain (PIDP)").

Table 16.5 summarizes the reports of BoNT treatment in patients with *trigeminal neuropathic pain with a history of trauma/dentomaxillofacial procedure (suggestive of PTTNP)* [103–110]. In these cases, applied BoNT doses ranged between 10 U and 250 U, but achievement of pain relief was satisfactory in most subjects. The available information indicated between four and ten injection points that were divided among the painful regions to fulfill the predetermined total doses. Different BoNT types such as onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and South Korean type A toxin (Meditoxin and Innotox) were used in these studies. Intraoral administration sites were more common in the facial gingiva and vestibular mucosa, but tooth socket, hard palate, and labial mucosa were also injected. Extraoral administrations included intradermal and intramuscular routes. Effects were reported as early as 3 days and as late as 1 month, lasting between 2 and 5 months. No serious long-term adverse events were observed in these cases. Of the 18 subjects reported in Table 16.5, there were a total of three female nonresponders [107, 109]. Two of them had a history of orthognathic surgery (20 U) and extraction of tooth #30 (10 U). The authors suggested the possibility that further repeat cycles might have achieved significant results in these patients [109]. The other subject, a 52-year-old female, was reported as having persistent idiopathic facial pain, but considering the history of endodontic therapy, we included her in this section. The time of initiation of the pain after her dental treatment was not stated. Following endodontic treatment of the mandibular left first molar and first premolar, pain developed in the left lower "hemiface" and gradually intensified and was referred to the maxillary left quadrant. During the next 5 years, she received a series of

Table 16.5 Studies on the use of botulinum neurotoxin for management of trigeminal neuropathic pain in patients with any history of trauma or dentomaxillofacial procedures, suggestive of post-traumatic trigeminal neuropathic pain

Author/year	Study type	Patients	Chief complaint	History of trauma/ procedure	BoNT	Dosage	Injection	Assessments	BoNT Outcome
Yoon et al. 2010 [103]	Case report	Female 62 y	"Electric-like discomfort" + numbness in left lower lip and chin exacerbated by washing, touching, cold	Four implants (#22, #24, #25, #27) 2 m earlier	Botox	10U	Middle chin (subcutaneous)	CST → reduced sensation in left lower lip and chin; CPT with a Neurometer®	CPT → change from 1st m, sustained to 2nd m Patient noticed reduced area at 1st m and slight pain decrease at 2nd m
Cuadrado et al. 2016 [104][a]	Clinical study	Male 31 y	Moderate to severe stabbing/ piercing pain in left max dental arch and missing molar + spread to left mand arch and hard palate	Endodontic surgery of #14 and extraction	BOTOX®	10 × 2.5U Total: 25U	Tooth socket (*N* = 1), left max (*N* = 3), and mand (*N* = 3) gingiva (facial papillae at pain area) and hard palate (*N* = 3)	Dental exam → no clinical, XRay or CT pathology; Blood tests including ESR → normal	Pain relief from 3rd d lasting to 4 m; almost complete relief after five cycles
Herrero Babiloni et al. 2016 [105]	Case report	Female 60 y	7 y deep-tissue constant ache in right V2 andV3 with 5–10 sharp episodes/d	Endodontic treatment of #29	BOTOX® with 2% lidocaine as solvent	6 × 17U Total: 102U	Posterior vestibular sulcus of right max molar region (*N* = 3) and attached gingiva around #29, (*N* = 2 buccal + 1 ling)	MRI → negative, NRS (pain), – Nasopalatine & local #29 block reduced pain	Pain relief from 1–2 w lasted to 2 m

García-Sáez et al. 2018 [110][b]	Quasi-experimental, prospective, open-label, non-controlled study	Male: 51 y	Pressing pain in missing #17 area and left lower lip with spread to left lower dental arch	Extraction of #17	Botox	8 × 2.5U Total: 20U	Left mand gingival facial papillae (*N* = 6) and left side of the lower lip (*N* = 2)	NRS (pain) Response rate: proportion of patients > 50% pain reduction	Pain relief from 14th d lasted to 4–5 m
		Female 48 y	Pressing pain in left max dental arch & missing molars with spread to left side of upper lip	Extraction of #14, #15, #16	Botox	8 × 2.5U Total: 20U	Left max gingival facial papillae (*N* = 6) and left side of the upper lip (*N* = 2)		Pain relief from 7thd lasted to 3 m
		Female 42 y	Throbbing pain in missing molar	Extraction of #18	Botox	4 × 2.5U Total: 10U	Left lower gingival facial papillae (*N* = 4)		Pain relief from 2nd d lasted to 3 m
		Female 77 y	Dull pain in missing molar with spread to left mand dental arch	Extraction of #19	Botox	6 × 2.5U Total: 15U	Left lower gingival facial papillae (*N* = 6)		Pain relief from 7th d lasted to 3 m
Borges et al. 2018 [107][c]	Case report	Female 52 y	Diffuse, pulsatile, shocking, low frequency/intensity pain in left mand hemiface, with referral to ipsilateral max with time Crises ➞ pulsatile, burning + allodynia and irradiation to the superior alveolar branch region	Endodontic treatment of #21 and #19, 5 y earlier, after which pain started and got worse	BoNT-A	Total: 200IU	NS	Continuous visual scale, DN4 ➞ positive for neuropathic, DSM-5, LSSI, SF-36, HADS, PSQI-BR	No improvement after BoNT injection

(continued)

Table 16.5 (continued)

Author/year	Study type	Patients	Chief complaint	History of trauma/ procedure	BoNT	Dosage	Injection	Assessments	BoNT Outcome
Kim et al. 2018 [108]	Retro-spective case series	Female 67 y	Pain in max left ant buccal vestibule+tightening of upper lip	Multiple maxillary dental implants	Dysport	Total: 250U	Upper part of mucosa	NS	Second injection of 250U was given 3 months later and the pain did not recur
		Female 52 y	Pain in left side of face, masseter, zygoma and TMJ area + left cheek excessive salivation	Facial nerve reconstruction during plastic surgery	Innotox	Total: 25U	Left masseter	NS	Pain reduced 2 w later but still present 2nd course started 6 m later, still had some pain 3rd course given 3 m later, pain was tolerable
		Female 62 y	Pain in right lower lip and chin	Exact source of trauma not specified	Meditoxin	Total: 100U	Intraoral	NS	Pain was relieved and 2nd course was given
		Female 71 y	Pain in left face, lip gingiva	Exact source of trauma not specified	Innotox	Total: 20U	Intraoral	NS	Pain relief
		Female 68 y	Facial pain	Exact source of trauma not specified	Dysport	Total: 250U	Temporalis	NS	Pain relief

Moreno-Hay et al. 2018 [109]	Case series	Male 73 y	Pain in left mand lateral incisor	Dental treatment #23	Botox	Total: 20U	Vestibular mucosa or attached gingiva, doses divided among three evenly distributed sites	VRS (pain)	Pain reduction >50%, from 7th d, lasting 5 w
		Female 63 y	Pain in max central incisors	Dental treatment #9	Botox	Total: 10U			Pain reduction >50%, from 12th d, lasting 6 w
		Female 21 y	Pain in mand central incisors	Orthognathic surgery	Botox	Total: 20U			No response
		Female 49 y	Pain in right mand premolar and 1st molar	Extraction #30	Botox	Total: 10U			No response
De la Torre Canales et al. 2020 [106]	Case report	Male 44 y	8 y pain in left mand molar area, exacerbated by eating, brushing, etc.	Extraction of #19, pain followed 4 m later	Botox	10 × 5U Total: 50U	Buccal gingiva apical to #19, extended over #18 and #20	VAS, QualST (↑ hypersensitive to touch and pinprick), PGIC, Inferior alveolar block reduced pain	Pain relief from 2nd w to 5th m; recurred at 6th m

AE adverse events, *ant* anterior, *BoNT* botulinum neurotoxin, *d* day, *CPT* current perception threshold, *CST* Clinical Sensory Test, *DN4* Douleur Neuropathique en 4, *DSM-5* Diagnostic and Statistical Manual of Mental Disorders, *HADS* Hospital Anxiety and Depression Scale, *ling* lingual, *LSSI* Lipp's stress symptoms inventory, *m* month, *Mand* mandible, *Max* maxilla, *NRS* numeric rating scale, *NS* not specified, *PGIC* Patients Global Impression of Change, *PSQI-BR* Pittsburgh Sleep Quality Index, *QualST* qualitative sensory tests, *SF12* 12-item short form questionnaire, *SF36* short form (36), *TMJ* temporomandibular joint, *VAS* visual analog scale, *VRS* Verbal Rating Scale (0–10), *w* week

[a] This was an open, noncontrolled clinical study with four patients, one of which had a history of a traumatic event, hence his inclusion in this Table. Please see Table 16.6 for information on other patients

[b] This study reported a total of nine patients, four of which were presented previously by the same authors in the study by Cuadrado et al. (second row). All patients of both studies are being reported in Tables 16.5 and 16.6

[c] This case has been reported as persistent idiopathic facial pain (exact duration of onset after endodontic treatment has not been stated). It is being included here only due to the history of endodontic treatment

Table 16.6 Studies using botulinum neurotoxin for management of trigeminal neuropathic pain in patients with no history of trauma or dentomaxillofacial procedures suggestive of persistent idiopathic facial/dentoalveolar pain

Author/ year	Study type	Patients	Chief complaint	BoNT	Dosage	Injection	Assessment	Outcome
Cuadrado et al. 2016 [104][a]	Clinical study	Female 72 y	Moderate, burning pain in paramedian max and mand dental arches with spread to upper lip	Botox	12 × 2.5U Total: 30U	Max gingiva (*N* = 4), mand gingival facial papillae (*N* = 4) and upper lip (*N* = 4)	Dental exam → no clinical, XRay or CT pathology; Blood tests including ESR → normal results	Pain relief from 10th d lasted to 3 m; complete relief after three cycles
		Female 52 y	Mild to severe, stabbing/burning pain in left mand paramedian dental arch with spread to chin	Botox	8 × 2.5U Total: 20U	Paramedian and left mand gingival facial papillae		Pain relief from 14th d lasted to 3/6 m; almost complete relief after two cycles
		Male 53 y	Mild to severe, stabbing/burning pain in right max dental arch with spread to preauricular area	Botox	6 × 2.5U Total: 15U	Max right gingival facial papillae		Pain relief from 7th d lasted to 2 m almost complete relief after two cycles
Kim et al. 2018 [108]	Retrospective case series	Female 70 y	Pain in right max ant gingiva	Meditoxin	Total: 120U	Intraoral	NS	Not effective
		Female 66 y	Pain in left max posterior gingiva	Dysport	Total: 20U	Intraoral	NS	Not effective
García-Sáez et al. 2018 [110][b]	Quasi-experimental, prospective, open-label, noncontrolled study	Male: 46 y	Electric, continuous pain in right mand dental arch with spread to ipsilateral mand angle	Botox	6 × 2.5U Total: 15U	Right mand gingival facial papillae	NRS (pain): Response rate: proportion of patients > 50% pain reduction	Pain relief from 15th d lasted to 3–6 m

Moreno-Hay, 2019 [109]	Case series	Female 53 y	Pain in left max 3rd molar	Botox	Total: 20U	Vestibular mucosa or attached gingiva, doses divided among three evenly distributed sites	VRS (pain)	No response
		Female 66 y	Pain in right max premolar/lateral incisor	Botox	Total: 25U			Pain reduction >50%, from 12th d, lasting 1 w
		Female 43 y	Pain in left mand 2nd premolar/molar	Botox	Total: 10U			Pain reduction (25%), from 14th d, lasting 8 w
		Female 51 y	Pain in left mand canine/incisors	Botox	Total: 10U			Pain reduction (40%), from 15th d, lasting 5 w

AE adverse events, *ant* anterior, *BoNT* botulinum neurotoxin, *d* day, *m* month, *Mand* mandible, *Max* maxilla, *NRS* numeric rating scale, *NS* not specified, *VAS* visual analogue scale, *VRS* Verbal Rating Scale (0–10), *w* week

[a] This was an open, noncontrolled clinical study with four patients, one of which had a history of a traumatic event. Please see Table 16.5 for information on that patient

[b]This study reported a total of nine patients, four of which were presented previously by the same authors in the study by Cuadrado et al. (first row). All patients of both studies are being reported in Tables 16.5 and 16.6

diagnoses and treatments with no relief. Despite administration of one of the highest BoNT doses found among the current reports (200 U), the subject's pain did not subside. Pain from pulp conditions and posterior teeth can be referred to the ipsilateral opposite jaw [111]. Additionally, persistent ectopic pain can develop following trauma to the mandibular nerve fibers and eventually disseminate to regions innervated by other untraumatized trigeminal nerve branches [112]. Based on the provided information, it is not clear whether the pain in this patient originated from her endodontic procedure but maybe the referral nature of the pain made BoNT treatment less effective. Similar observations regarding the reduced efficacy of BoNT on referred myofascial pain were discussed above under treatment of TMD pain.

Intraoral injections are mostly safe and used routinely in dental practice. However, it has been suggested to be cautious during intraoral injection of BoNT by reducing the dosage and number of injections as much as possible but enough to achieve the desired effect [105].

Comments

Despite the encouraging results on BoNT efficacy in the treatment of *trigeminal neuropathic pain with a history of trauma (suggestive of PTTNP)*, drawing definitive conclusions on dosage and number of injection sites to use as a guideline is not possible at this point due to the limited number of available studies. Controlled and blinded studies are needed to define the efficacy of BoNT treatment in PTTNP.

Idiopathic Orofacial Pain

Idiopathic orofacial pain is defined as persistent, poorly localized pain of unknown cause with moderate intensity occurring on one or both sides of the face or oral cavity in the distribution area of ≥1 of the trigeminal branches identified as "burning," "pressing," or "dull" [9].

Persistent Idiopathic Facial Pain (PIFP)

Persistent Idiopathic Dentoalveolar Pain (PIDP)

These disorders have been classified as a single entity in ICHD-3 but are considered separately in ICOP [9, 102]. Based on the existing literature on BoNT, they will be considered together for convenience.

Definition, Classification, and Epidemiology

Persistent pain in the face not following a peripheral nerve distribution or occurring unilaterally in the dentoalveolar complex localized to a tooth or alveolar bone rarely in more than one site, recurring for >2 h/day for >3 months, with no detectable clinical, radiographic, or local cause, is regarded as PIFP and PIDP, respectively [9]. The further classifications of these entities are beyond the scope of this discussion. Considering the different classifications, terminology, and diagnostic criteria, an exact estimate of its prevalence is difficult to obtain, and ranges between 0.03% and 1% have been reported with a higher incidence in 40- to 50-year-old females [1, 113].

Management of Persistent Idiopathic Facial and Dentoalveolar Pain

Due to the ambiguous nature of these disorders, a specific treatment has not been developed, and the level of evidence for the suggested therapies, like low-level laser, tricyclic antidepressants, duloxetine, venlafaxine, and anticonvulsants, is low [1].

Efficacy of BoNT in the Treatment of Persistent Idiopathic Facial and Dentoalveolar Pain

The number of investigations on BoNT effectiveness in PIFP and PIDP is scarce, and there are no placebo-controlled, blinded clinical trials. The studies are limited to case reports, case series, and open-label trials. Additionally, as stated above, due to overlaps in definition with PTTNP and lack of detailed data on patient characteristics in the existing reports, it would be difficult to collectively evaluate BoNT studies on PIFP/PIDP management. Table 16.6 illustrates cases of BoNT therapy in patients with *trigeminal neuropathic pain without a history of trauma/dentomaxillofacial procedures (suggestive of PIFP/PIDP)*. There were a total of ten cases reported in four studies [104, 108–110] that used 10 U–30 U BOTOX®, Meditoxin, or Dysport to inject into 6–12 points distributed in the gingiva. Of the treated cases, three patients did not respond, and two patients had less than 50% pain reduction, meaning that suboptimal results were obtained in 50% of patients.

Comment

With the small number of cases and lack of double-blind comparisons with placebo, the efficacy of BoNT in the treatment of *trigeminal neuropathic pain without a history of trauma/dentomaxillofacial procedure (suggestive of PIFP/PIDP)* is unclear at this stage, but it seems that the responsiveness of patients to toxin administration is not as favorable as the other neuropathic pain subgroups.

Burning Mouth Syndrome

Definition, Classification, and Epidemiology

ICOP describes BMS as a burning or dysesthetic feeling lacking an apparent local or systemic cause that occurs >2 h/day for over 3 months ("probable BMS" if less than 3 months). In addition, the pain has to be "burning" and "superficial" for diagnosis. This disorder is further divided into BMS with and without somatosensory changes, based on the results of quantitative sensory testing [9].

The global prevalence of BMS is 1.73% worldwide and 7.72% in dental clinics, with a higher prevalence in Europe (5.58%) and North America (1.10%) compared to Asia (1.05%). It occurs almost three times more often in women and is more prevalent in individuals >50 years of age [114].

There has been controversy regarding different aspects of this entity including nomenclature (replacing BMS with BM "disorder"), research diagnostic criteria, duration of symptoms, and pathophysiology [115, 116]. An important question that can influence treatment options is whether this disease is a neuropathic pain disorder, with some classification systems considering it as such [1, 7, 117]. Central and peripheral neuropathies have both been variably implicated in BMS. The former is associated with disruption of the dopaminergic or serotoninergic systems, while the latter involves peripheral neuropathy of the small-diameter fibers in the oral mucosa [117]. ICOP has also suggested the possibility of BMS being considered as a neuropathic pain condition [9].

Management of Burning Mouth Syndrome

There is no uniform evidence-based treatment strategy for BMS, but the most important initiative would be a correct diagnosis and ruling out all other entities with similar symptoms. Starting from the most conservative options like masticatory muscle exercise and hot pack, ultrasound and physical therapy are recommended. Pharmacotherapy with systemic or local agents like antidepressants, gabapentin, clonazepam, lycopene, lafutidine, and capsaicin and psychological treatments have been administered in these patients with variable results [6].

Efficacy of BoNT in the Treatment of Burning Mouth Syndrome

The number of studies on BoNT injection in BMS patients is scarce (Table 16.7), and the information provided on diagnostic criteria and treatment is insufficient [118–120]. The dosage used for effective management has ranged from 50 to 100 U, which was injected into masticatory muscles, the tongue, and lip, with effects starting from 48 hto 3 weeks later and lasting up to 20 weeks with no significant side effects.

Table 16.7 Outline of studies using botulinum neurotoxin for the management of burning mouth syndrome

Authors	Patients	History	Symptoms	BoNT	Dose	Injection site	Outcome	Time to effect	Lasting effect
Seo et al. 2009 [118]	*N* = 1 Female 54 y	Neuroleptic therapy	Tongue dyskinesia + severe oral burning 5 y after therapy for neuroleptic therapy	BoNT-A	50U	Tongue muscles	Both issues improved	10 d	NS, injections given each month for 2 y
Restivo et al. 2017 [119]	*N* = 6 Females: 5[a] Male: 1 67–76 y	Diabetes in 3 patients	Anterior 2/3 of tongue + lower lip for at least 6 m	Inco-botulinumtoxinA	16U	Bilateral lower lip + bilateral anterolateral tongue	Initial 60–90 VAS reduced to 0	48h	12–20 w
Kwon and Park 2020 [120]	*N* = 1 Female 60 y	N/S	Burning + dryness	Meditoxin	100U	60U in both masseters + 40U in both temporalis	Initial 5 NRS reduced to 2	3 w	N/S

d day, *h* hour, *NRS* numeric rating scale, *NS* not specified, *VAS* visual analog scale, *w* week, *y* year

[a] Two females initially received saline as placebo with no improvement after 4 weeks

The logic behind using this toxin relies on both its muscle relaxant and antinociceptive effects. Musculoskeletal issues and tension of the lingual muscles have been proposed as possible triggering factors for tongue pain [121, 122]. Parafunctional habits and masticatory muscle tenderness upon palpation are relatively common among BMS patients. Hypotheses like habit-induced microtrauma causing neuropathic alterations in the tongue and lingual nerve compression due to entrapment in the lateral pterygoid muscle have been suggested for the possibility of musculoskeletal involvement in BMS [120, 123].

As for the justification of the antinociceptive effect of BoNT in BMS, it should be noted that BoNT-A inhibits the activity and membrane translocation of transient receptor potential vanilloid-1 (TRPV1), and its effect has been shown in several pain models [124]. In BMS, there is a reduction of C-fibers in the lingual mucosa causing upregulation of TRPV1 (among other factors) in the remaining fibers, each responding to specific stimulations [117].

Comment

Based on the extremely limited number of reports on the use of BoNT for managing BMS, it is not possible to form a definitive opinion on its efficacy. However, considering the refractory nature of the disease, the favorable reports, and the safety of BoNT, it seems that this toxin may be a potential option for BMS treatment and warrants further investigation.

Case Report: Courtesy of B. Jabbari, MD [75]

A healthy 60-year-old man presented with significant painful hypersensitivity to touch on the gingiva adjacent to an extraction site with three missing left molars. The allodynia developed 3 years ago following the extractions and was described as attacks of severe and jabbing pain that radiated to the upper lip on the same side. The paroxysms occurred several times a day with an intensity of 9 or 10 on VAS and prevented him from comfortable brushing. He was currently on 600 mg gabapentin, q.i.d. which was not effective, similar to his past analgesic medications.

The allodynia on the gingiva, over and anterior to the extraction site, was confirmed on examination (Fig. 16.1), and he was injected intramucosally with 10 U (2.5 U × 4 points) of onaA in the painful area, 2–3 mm below the surface. Based on the preceding discussion, the pain could be classified as trigeminal neuropathic pain with a history of dentomaxillofacial procedure (suggestive of PTTNP). He reported distinct improvement of pain and discontinuation of the paroxysms after 7 days. The effects lasted up to 6 months, and a second round of treatment was administered at the patient's request, which yielded the same efficacy. He recorded a "very much improved" answer in PGIC (Fig. 16.1).

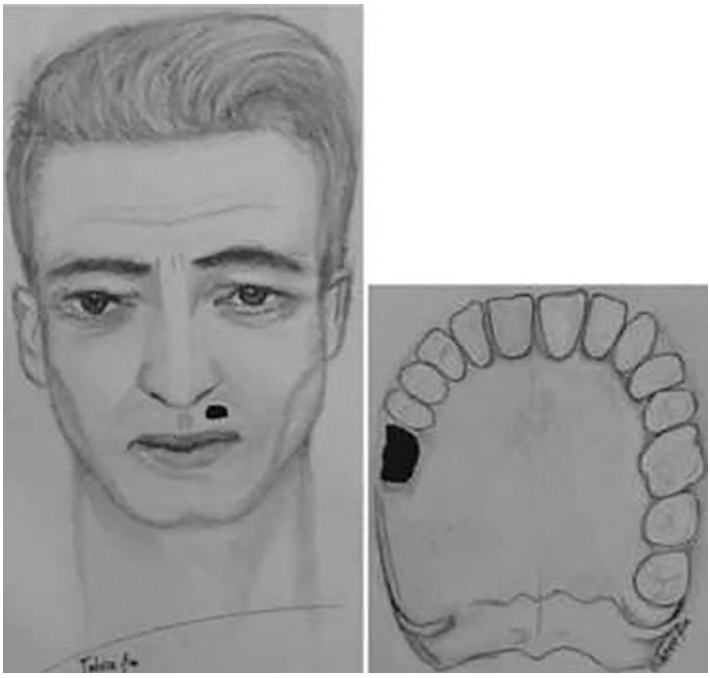

Fig. 16.1 Regions of allodynia on the gingiva covering an extraction site, with radiation to the upper lip on the same side. A total of 10 U (4 × 2.5 U) onaA was administered into areas demarcated with black ink. (Drawing courtesy of Damoun Safarpour, MD)

References

1. Korczeniewska OA, France K, Khan J, Greenberg MS, Benoliel R, Eliav E. Neuropathic Orofacial Pain. In: Glick M, Greenberg MS, Lockhart PB, Challacombe SJ, editors. Burket's Oral Medicine 13th ed. Wiley; 2021.p. 419–52.
2. Nagakura Y, Nagaoka S, Kurose T. Potential molecular targets for treating neuropathic orofacial pain based on current findings in animal models. Int J Mol Sci. 2021;22(12):6406. https://doi.org/10.3390/ijms22126406. PMID: 34203854; PMCID: PMC8232571
3. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003–7. https://doi.org/10.1097/j.pain.0000000000000160. PMID: 25844555; PMCID: PMC4450869
4. Ananthan S, Benoliel R. Chronic orofacial pain. J Neural Transm (Vienna). 2020;127(4):575–88. https://doi.org/10.1007/s00702-020-02157-3. Epub 2020 Mar 4. PMID: 32130516
5. Benoliel R, Svensson P, Evers S, Wang SJ, Barke A, Korwisi B, Rief W, Treede RD. IASP taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic secondary headache or orofacial pain. Pain. 2019;160(1):60–8. https://doi.org/10.1097/j.pain.0000000000001435. PMID: 30586072

6. Tait RC, Ferguson M, Herndon CM. Chronic orofacial pain: burning mouth syndrome and other neuropathic disorders. J Pain Manag Med. 2017;3(1):120. Epub 2017 Jan 30. PMID: 28638895; PMCID: PMC5475277.
7. Sharav Y, Benoliel R, editors. Orofacial pain and headache. Quintessence Publishing Company, Incorporated; 2015.
8. Kennedy R, Abd-Elsayed A. The International Association for the Study of Pain (IASP) classification of chronic pain syndromes. In: Pain. Cham: Springer; 2019. p. 1101–3.
9. International Classification of Orofacial Pain. 1st edition (ICOP). Cephalalgia. 2020;40(2):129–221. https://doi.org/10.1177/0333102419893823.
10. Muñoz Lora VR, Del Bel Cury AA, Jabbari B, Lacković Z. Botulinum toxin type a in dental medicine. J Dent Res. 2019;98(13):1450–7. https://doi.org/10.1177/0022034519875053. Epub 2019 Sep 18. PMID: 31533008
11. Ettlin DA, Napimoga MH, Meira E, Cruz M, Clemente-Napimoga JT. Orofacial musculoskeletal pain: an evidence-based bio-psycho-social matrix model. Neurosci Biobehav Rev. 2021;128:12–20. https://doi.org/10.1016/j.neubiorev.2021.06.008. Epub 2021 Jun 9. PMID: 34118294
12. Jessri M, Sultan AS, Tavares T, Schug S. Central mechanisms of pain in orofacial pain patients: implications for management. J Oral Pathol Med. 2020;49(6):476–83. https://doi.org/10.1111/jop.13062. Epub 2020 Jul 2. PMID: 32539196
13. Sessle BJ. Chronic orofacial pain: models, mechanisms, and genetic and related environmental influences. Int J Mol Sci. 2021;22(13):7112. https://doi.org/10.3390/ijms22137112. PMID: 34281164; PMCID: PMC8268972
14. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF, International RDC/TMD Consortium Network, International association for Dental Research; Orofacial Pain Special Interest Group, International Association for the Study of Pain. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†. J Oral Facial Pain Headache. 2014;28(1):6–27. https://doi.org/10.11607/jop.1151. PMID: 24482784; PMCID: PMC4478082
15. Gil-Martínez A, Paris-Alemany A, López-de-Uralde-Villanueva I, La Touche R. Management of pain in patients with temporomandibular disorder (TMD): challenges and solutions. J Pain Res. 2018;11:571–87. https://doi.org/10.2147/JPR.S127950. PMID: 29588615; PMCID: PMC5859913
16. Nouged E, Dajani J, Ku B, Al-Eryani K, Padilla M, Enciso R. Local anesthetic injections for the short-term treatment of head and neck myofascial pain syndrome: a systematic review with meta-analysis. J Oral Facial Pain Headache. 2019;33(2):183–98. https://doi.org/10.11607/ofph.2277. Epub 2019 Mar 20. PMID: 30893405
17. Schwartz M, Freund B. Treatment of temporomandibular disorders with botulinum toxin. Clin J Pain. 2002;18(6 Suppl):S198–203. https://doi.org/10.1097/00002508-200211001-00013. PMID: 12569969
18. de Lima MC, Rizzatti Barbosa CM, Duarte Gavião MB, Ferreira Caria PH. Is low dose of botulinum toxin effective in controlling chronic pain in sleep bruxism, awake bruxism, and temporomandibular disorder? Cranio. 2021:1–8. https://doi.org/10.1080/08869634.2021.1973215. Epub ahead of print. PMID: 34488556
19. Bogucki ZA, Kownacka M. Clinical aspects of the use of botulinum toxin type a in the treatment of dysfunction of the masticatory system. Adv Clin Exp Med. 2016;25(3):569–73. https://doi.org/10.17219/acem/41923. PMID: 27629747
20. Batifol D, Huart A, Finiels PJ, Nagot N, Jammet P. Effect of intra-articular botulinum toxin injections on temporo-mandibular joint pain. J Stomatol Oral Maxillofac Surg.

2018;119(4):319–24. https://doi.org/10.1016/j.jormas.2018.06.002. Epub 2018 Jun 8. PMID: 29885911

21. Najafi S, Sanati E, Khademi M, Abdorrazaghi F, Mofrad RK, Rezasoltani Z. Intra-articular botulinum toxin type A for treatment of knee osteoarthritis: clinical trial. Toxicon. 2019;165:69–77. https://doi.org/10.1016/j.toxicon.2019.04.003. Epub 2019 Apr 14. PMID: 30995453
22. De la Torre CG, Alvarez-Pinzon N, Muñoz-Lora VRM, Vieira Peroni L, Farias Gomes A, Sánchez-Ayala A, Haiter-Neto F, Manfredini D, Rizzatti-Barbosa CM. Efficacy and safety of botulinum toxin type a on persistent myofascial pain: a randomized clinical trial. Toxins (Basel). 2020;12(6):395. https://doi.org/10.3390/toxins12060395. PMID: 32549196; PMCID: PMC7354430
23. Patel AA, Lerner MZ, Blitzer A. IncobotulinumtoxinA injection for temporomandibular joint disorder. Ann Otol Rhinol Laryngol. 2017;126(4):328–33. https://doi.org/10.1177/0003489417693013. Epub 2017 Feb 1. PMID: 28290229
24. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008;71(20):1634–8. https://doi.org/10.1212/01.wnl.0000336533.19610.1b. PMID: 19001254
25. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology. 2008;71(20):1639–43. https://doi.org/10.1212/01.wnl.0000336535.27773.c0. PMID: 19001255
26. Awan KH, Patil S, Alamir AWH, Maddur N, Arakeri G, Carrozzo M, Brennan PA. Botulinum toxin in the management of myofascial pain associated with temporomandibular dysfunction. J Oral Pathol Med. 2019;48(3):192–200. https://doi.org/10.1111/jop.12822. Epub 2019 Jan 25. PMID: 30604895
27. Thambar S, Kulkarni S, Armstrong S, Nikolarakos D. Botulinum toxin in the management of temporomandibular disorders: a systematic review. Br J Oral Maxillofac Surg. 2020;58(5):508–19. https://doi.org/10.1016/j.bjoms.2020.02.007. Epub 2020 Mar 3. PMID: 32143934
28. Machado D, Martimbianco ALC, Bussadori SK, Pacheco RL, Riera R, Santos EM. Botulinum toxin type A for painful temporomandibular disorders: systematic review and meta-analysis. J Pain. 2020;21(3–4):281–93. https://doi.org/10.1016/j.jpain.2019.08.011. Epub 2019 Sep 9. PMID: 31513934
29. Khawaja SN, Scrivani SJ, Holland N, Keith DA. Effectiveness, safety, and predictors of response to botulinum toxin type a in refractory masticatory myalgia: a retrospective study. J Oral Maxillofac Surg. 2017;75(11):2307–15. https://doi.org/10.1016/j.joms.2017.01.031. PMID: 29078865
30. Abboud WA, Hassin-Baer S, Joachim M, Givol N, Yahalom R. Localized myofascial pain responds better than referring myofascial pain to botulinum toxin injections. Int J Oral Maxillofac Surg. 2017;46(11):1417–23. https://doi.org/10.1016/j.ijom.2017.04.020. Epub 2017 May 15. PMID: 28521968
31. Villa S, Raoul G, Machuron F, Ferri J, Nicot R. Improvement in quality of life after botulinum toxin injection for temporomandibular disorder. J Stomatol Oral Maxillofac Surg. 2019;120(1):2–6. https://doi.org/10.1016/j.jormas.2018.10.007. Epub 2018 Oct 29. PMID: 30385428
32. Montes-Carmona JF, Gonzalez-Perez LM, Infante-Cossio P. Treatment of localized and referred masticatory myofascial pain with botulinum toxin injection. Toxins (Basel). 2020;13(1):6. https://doi.org/10.3390/toxins13010006. PMID: 33374687; PMCID: PMC7822413
33. Chaurand J, Godínez-Victoria M, Tellez-Girón A, Facio-Umaña JA, Jimenez-Ponce F. Incobotulinum toxin type A for treatment of chronic myofascial pain. J Oral Sci. 2020;63(1):37–40. https://doi.org/10.2334/josnusd.20-0090. Epub 2020 Dec 9. PMID: 33298638

34. Yoshida K. Effects of botulinum toxin type a on pain among trigeminal neuralgia, myofascial temporomandibular disorders, and Oromandibular dystonia. Toxins (Basel). 2021;13(9):605. https://doi.org/10.3390/toxins13090605. PMID: 34564609; PMCID: PMC8471742
35. Goldstein G, DeSantis L, Goodacre C. Bruxism: best evidence consensus statement. J Prosthodont. 2021;30(S1):91–101. https://doi.org/10.1111/jopr.13308. PMID: 33331675
36. De la Torre CG, Poluha RL, Lora VM, Araújo Oliveira Ferreira DM, Stuginski-Barbosa J, Bonjardim LR, Cury AADB, Conti PCR. Botulinum toxin type A applications for masticatory myofascial pain and trigeminal neuralgia: what is the evidence regarding adverse effects? Clin Oral Investig. 2019;23(9):3411–21. https://doi.org/10.1007/s00784-019-03026-4. Epub 2019 Jul 24. PMID: 31342244
37. Kim HS, Yun PY, Kim YK. A clinical evaluation of botulinum toxin-a injections in the temporomandibular disorder treatment. Maxillofac Plast Reconstr Surg. 2016;38(1):5. https://doi.org/10.1186/s40902-016-0051-7. PMID: 26855937; PMCID: PMC4729782
38. Thomas NJ, Aronovich S. Does adjunctive botulinum toxin a reduce pain scores when combined with temporomandibular joint arthroscopy for the treatment of concomitant temporomandibular joint arthralgia and myofascial pain? J Oral Maxillofac Surg. 2017;75(12):2521–8. https://doi.org/10.1016/j.joms.2017.04.011. Epub 2017 Apr 19. PMID: 28500876
39. Altaweel AA, Elsayed SA, Baiomy AABA, Abdelsadek SE, Hyder AA. Extraoral versus intraoral botulinum toxin type a injection for management of temporomandibular joint disc displacement with reduction. J Craniofac Surg. 2019;30(7):2149–53. https://doi.org/10.1097/SCS.0000000000005658. PMID: 31232992
40. Lora VR, Clemente-Napimoga JT, Abdalla HB, Macedo CG, Canales GT, Barbosa CM. Botulinum toxin type A reduces inflammatory hypernociception induced by arthritis in the temporomadibular joint of rats. Toxicon. 2017;129:52–7. https://doi.org/10.1016/j.toxicon.2017.02.010. Epub 2017 Feb 14. PMID: 28209481
41. Lobbezoo F, Ahlberg J, Glaros AG, Kato T, Koyano K, Lavigne GJ, de Leeuw R, Manfredini D, Svensson P, Winocur E. Bruxism defined and graded: an international consensus. J Oral Rehabil. 2013;40(1):2–4. https://doi.org/10.1111/joor.12011. Epub 2012 Nov 4. PMID: 23121262
42. Lobbezoo F, Ahlberg J, Raphael KG, Wetselaar P, Glaros AG, Kato T, Santiago V, Winocur E, De Laat A, De Leeuw R, Koyano K, Lavigne GJ, Svensson P, Manfredini D. International consensus on the assessment of bruxism: report of a work in progress. J Oral Rehabil. 2018;45(11):837–44. https://doi.org/10.1111/joor.12663. Epub 2018 Jun 21. PMID: 29926505; PMCID: PMC6287494
43. Manfredini D, Ahlberg J, Wetselaar P, Svensson P, Lobbezoo F. The bruxism construct: from cut-off points to a continuum spectrum. J Oral Rehabil. 2019;46(11):991–7. https://doi.org/10.1111/joor.12833. Epub 2019 Jul 2. PMID: 31264730
44. Boscato N, Nascimento GG, Leite FRM, Horta BL, Svensson P, Demarco FF. Role of occlusal factors on probable bruxism and orofacial pain: data from the 1982 Pelotas birth cohort study. J Dent. 2021;113:103788. https://doi.org/10.1016/j.jdent.2021.103788. Epub 2021 Aug 21. PMID: 34425171
45. Castrillon EE, Exposto FG. Sleep bruxism and pain. Dent Clin N Am. 2018;62(4):657–63. https://doi.org/10.1016/j.cden.2018.06.003. Epub 2018 Aug 14. PMID: 30189988
46. Muzalev K, van Selms MK, Lobbezoo F. No dose-response association between self-reported bruxism and pain-related temporomandibular disorders: a retrospective study. J Oral Facial Pain Headache. 2018;32(4):375–80. https://doi.org/10.11607/ofph.2090. PMID: 30365573
47. Van Zandijcke M, Marchau MM. Treatment of bruxism with botulinum toxin injections. J Neurol Neurosurg Psychiatry. 1990;53(6):530. https://doi.org/10.1136/jnnp.53.6.530. PMID: 2380736; PMCID: PMC1014218
48. Ågren M, Sahin C, Pettersson M. The effect of botulinum toxin injections on bruxism: a systematic review. J Oral Rehabil. 2020;47(3):395–402. https://doi.org/10.1111/joor.12914. Epub 2019 Dec 15. PMID: 31769044

49. Baldwin MC, Liu ZJ, Rafferty KL, Keith A, Tamasas B, Kaiyala K, Herring SW. Botulinum toxin in the masseter muscle: lingering effects of denervation. Anat Rec (Hoboken). 2021; https://doi.org/10.1002/ar.24756. Epub ahead of print. PMID: 34486243
50. Alwayli HM, Abdulrahman BI, Rastogi S. Does botulinum toxin have any role in the management of chronic pain associated with bruxism? Cranio. 2021:1–8. https://doi.org/10.1080/08869634.2021.1949536. Epub ahead of print. PMID: 34259618
51. Klasser GD, Rei N, Lavigne GJ. Sleep bruxism etiology: the evolution of a changing paradigm. J Can Dent Assoc. 2015;81:f2. PMID: 25633110
52. Asutay F, Atalay Y, Asutay H, Acar AH. The evaluation of the clinical effects of botulinum toxin on nocturnal bruxism. Pain Res Manag. 2017;2017:6264146. https://doi.org/10.1155/2017/6264146. Epub 2017 Jul 5. PMID: 28757802; PMCID: PMC5516743
53. Yurttutan ME, Tütüncüler Sancak K, Tüzüner AM. Which treatment is effective for bruxism: occlusal splints or botulinum toxin? J Oral Maxillofac Surg. 2019;77(12):2431–8. https://doi.org/10.1016/j.joms.2019.06.005. Epub 2019 Jun 19. PMID: 31302066
54. Ondo WG, Simmons JH, Shahid MH, Hashem V, Hunter C, Jankovic J. Onabotulinum toxin-A injections for sleep bruxism: a double-blind, placebo-controlled study. Neurology. 2018;90(7):e559–64. https://doi.org/10.1212/WNL.0000000000004951. Epub 2018 Jan 17. PMID: 29343468
55. Al-Wayli H. Treatment of chronic pain associated with nocturnal bruxism with botulinum toxin. A prospective and randomized clinical study. J Clin Exp Dent. 2017;9(1):e112–7. https://doi.org/10.4317/jced.53084. PMID: 28149474; PMCID: PMC5268105
56. Kaya DI, Ataoglu H. Botulinum toxin treatment of temporomandibular joint pain in patients with bruxism: a prospective and randomized clinical study. Niger J Clin Pract. 2021;24(3):412–7. https://doi.org/10.4103/njcp.njcp_251_20. PMID: 33723117
57. Jadhao VA, Lokhande N, Habbu SG, Sewane S, Dongare S, Goyal N. Efficacy of botulinum toxin in treating myofascial pain and occlusal force characteristics of masticatory muscles in bruxism. Indian J Dent Res. 2017;28(5):493–7. https://doi.org/10.4103/ijdr.IJDR_125_17. PMID: 29072209
58. Shim YJ, Lee HJ, Park KJ, Kim HT, Hong IH, Kim ST. Botulinum toxin therapy for managing sleep bruxism: a randomized and placebo-controlled trial. Toxins (Basel). 2020;12(3):168. https://doi.org/10.3390/toxins12030168. PMID: 32182879; PMCID: PMC7150956
59. De la Torre Canales G, Câmara-Souza MB, do Amaral CF, Garcia RC, Manfredini D. Is there enough evidence to use botulinum toxin injections for bruxism management? A systematic literature review. Clin Oral Investig. 2017;21(3):727–34. https://doi.org/10.1007/s00784-017-2092-4. Epub 2017 Mar 2. PMID: 28255752
60. Khan M, Nishi SE, Hassan SN, Islam MA, Gan SH. Trigeminal neuralgia, glossopharyngeal neuralgia, and myofascial pain dysfunction syndrome: an update. Pain Res Manag. 2017;2017:7438326. https://doi.org/10.1155/2017/7438326. Epub 2017 Jul 30. PMID: 28827979; PMCID: PMC5554565
61. Helmstaedter V, Wittekindt C, Huttenbrink KB, Guntinas-Lichius O. Safety and efficacy of botulinum toxin therapy in otorhinolaryngology: experience from 1,000 treatments. Laryngoscope. 2008;118(5):790–6. https://doi.org/10.1097/MLG.0b013e318162cafc. PMID: 18300708
62. Bendtsen L, Zakrzewska JM, Abbott J, Braschinsky M, Di Stefano G, Donnet A, Eide PK, Leal PRL, Maarbjerg S, May A, Nurmikko T, Obermann M, Jensen TS, Cruccu G. European academy of neurology guideline on trigeminal neuralgia. Eur J Neurol. 2019;26(6):831–49. https://doi.org/10.1111/ene.13950. Epub 2019 Apr 8. PMID: 30860637
63. Bendtsen L, Zakrzewska JM, Heinskou TB, Hodaie M, Leal PRL, Nurmikko T, Obermann M, Cruccu G, Maarbjerg S. Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. Lancet Neurol. 2020;19(9):784–96. https://doi.org/10.1016/S1474-4422(20)30233-7. PMID: 32822636

64. Araya EI, Claudino RF, Piovesan EJ, Chichorro JG. Trigeminal neuralgia: basic and clinical aspects. Curr Neuropharmacol. 2020;18(2):109–19. https://doi.org/10.2174/1570159X17666191010094350. PMID: 31608834; PMCID: PMC7324879
65. Liu J, Xu YY, Zhang QL, Luo WF. Efficacy and safety of botulinum toxin type A in treating patients of advanced age with idiopathic trigeminal neuralgia. Pain Res Manag. 2018;2018:7365148. https://doi.org/10.1155/2018/7365148. PMID: 29849847; PMCID: PMC5907496
66. Morra ME, Elgebaly A, Elmaraezy A, Khalil AM, Altibi AM, Vu TL, Mostafa MR, Huy NT, Hirayama K. Therapeutic efficacy and safety of botulinum toxin A therapy in trigeminal neuralgia: a systematic review and meta-analysis of randomized controlled trials. J Headache Pain. 2016;17(1):63. https://doi.org/10.1186/s10194-016-0651-8. Epub 2016 Jul 5. PMID: 27377706; PMCID: PMC4932020
67. Matak I, Bach-Rojecky L, Filipović B, Lacković Z. Behavioral and immunohistochemical evidence for central antinociceptive activity of botulinum toxin a. Neuroscience. 2011;186:201–7. https://doi.org/10.1016/j.neuroscience.2011.04.026. Epub 2011 Apr 20. PMID: 21539899
68. Wu C, Xie N, Lian Y, Xu H, Chen C, Zheng Y, Chen Y, Zhang H. Central antinociceptive activity of peripherally applied botulinum toxin type A in lab rat model of trigeminal neuralgia. Springerplus. 2016;5:431. https://doi.org/10.1186/s40064-016-2071-2. PMID: 27104119; PMCID: PMC4828356
69. Waskitho A, Yamamoto Y, Raman S, Kano F, Yan H, Raju R, Afroz S, Morita T, Ikutame D, Okura K, Oshima M, Yamamoto A, Baba O, Matsuka Y. Peripherally administered botulinum toxin type a localizes bilaterally in trigeminal ganglia of animal model. Toxins (Basel). 2021;13(10):704. https://doi.org/10.3390/toxins13100704. PMID: 34678997; PMCID: PMC8541196
70. Rubis A, Juodzbalys G. The use of botulinum toxin A in the Management of Trigeminal Neuralgia: a systematic literature review. J Oral Maxillofac Res. 2020;11(2):e2. https://doi.org/10.5037/jomr.2020.11202. PMID: 32760475; PMCID: PMC7393930
71. Ostrowski H, Roszak J, Komisarek O. Botulinum toxin type A as an alternative way to treat trigeminal neuralgia: a systematic review. Neurol Neurochir Pol. 2019;53(5):327–34. https://doi.org/10.5603/PJNNS.a2019.0030. Epub 2019 Aug 9. PMID: 31397877
72. Shackleton T, Ram S, Black M, Ryder J, Clark GT, Enciso R. The efficacy of botulinum toxin for the treatment of trigeminal and postherpetic neuralgia: a systematic review with meta-analyses. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(1):61–71. https://doi.org/10.1016/j.oooo.2016.03.003. Epub 2016 Mar 15. PMID: 27260275
73. Hu Y, Guan X, Fan L, Li M, Liao Y, Nie Z, Jin L. Therapeutic efficacy and safety of botulinum toxin type A in trigeminal neuralgia: a systematic review. J Headache Pain. 2013;14(1):72. https://doi.org/10.1186/1129-2377-14-72. PMID: 23964790; PMCID: PMC3765392
74. Egeo G, Fofi L, Barbanti P. Botulinum neurotoxin for the treatment of neuropathic pain. Front Neurol. 2020;11:716. https://doi.org/10.3389/fneur.2020.00716. PMID: 32849195; PMCID: PMC7431775
75. Jabbari B. Botulinum toxin treatment of chronic facial pain: trigeminal neuralgia, temporomandibular disorders, and dental-related pain. In: Botulinum toxin treatment of pain disorders. New York: Springer; 2015. p. 137–52. ISBN 978-1-4939-2501-8.
76. Zúñiga C, Piedimonte F, Díaz S, Micheli F. Acute treatment of trigeminal neuralgia with onabotulinum toxin A. Clin Neuropharmacol. 2013;36(5):146–50. https://doi.org/10.1097/WNF.0b013e31829cb60e. PMID: 24045604
77. Li S, Lian YJ, Chen Y, Zhang HF, Ma YQ, He CH, Wu CJ, Xie NC, Zheng YK, Zhang Y. Therapeutic effect of Botulinum toxin-A in 88 patients with trigeminal neuralgia with 14-month follow-up. J Headache Pain. 2014;15(1):43. https://doi.org/10.1186/1129-2377-15-43. PMID: 24952600; PMCID: PMC4077143

78. Zhang H, Lian Y, Ma Y, Chen Y, He C, Xie N, Wu C. 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. https://doi.org/10.1186/1129-2377-15-65. PMID: 25263254; PMCID: PMC4194456
79. Xia JH, He CH, Zhang HF, Lian YJ, Chen Y, Wu CJ, Ma YQ. Botulinum toxin A in the treatment of trigeminal neuralgia. Int J Neurosci. 2016;126(4):348–53. https://doi.org/10.3109/00207454.2015.1019624. Epub 2015 Aug 18. PMID: 26000810
80. Türk Börü Ü, Duman A, Bölük C, Coşkun Duman S, Taşdemir M. Botulinum toxin in the treatment of trigeminal neuralgia: 6-month follow-up. Medicine (Baltimore). 2017;96(39):e8133. https://doi.org/10.1097/MD.0000000000008133. PMID: 28953646; PMCID: PMC5626289
81. Zhang H, Lian Y, Xie N, Chen C, Zheng Y. Single-dose botulinum toxin type a compared with repeated-dose for treatment of trigeminal neuralgia: a pilot study. J Headache Pain. 2017;18(1):81. https://doi.org/10.1186/s10194-017-0793-3. PMID: 28799056; PMCID: PMC5552618
82. Gorimanipalli B, Elavarasi A, Goyal V, Goyal C, Shukla G, Behari M. Sustained effect of repeated botulinum toxin type A injections in trigeminal neuralgia. Neurol Clin Neurosci. 2019;7(6):318–21.
83. Caldera MC, Senanayake SJ, Perera SP, Perera NN, Gamage R, Gooneratne IK. Efficacy of botulinum toxin type A in trigeminal neuralgia in a South Asian Cohort. J Neurosci Rural Pract. 2018;9(1):100–5. https://doi.org/10.4103/jnrp.jnrp_346_17. PMID: 29456352; PMCID: PMC5812131
84. Crespi J, Bratbak D, Dodick DW, Matharu M, Jamtøy KA, Tronvik E. Pilot study of injection of OnabotulinumtoxinA toward the sphenopalatine ganglion for the treatment of classical trigeminal neuralgia. Headache. 2019;59(8):1229–39. https://doi.org/10.1111/head.13608. Epub 2019 Jul 25. PMID: 31342515; PMCID: PMC6771650
85. Zhang H, Lian Y, Xie N, Cheng X, Chen C, Xu H, Zheng Y. Factors affecting the therapeutic effect of botulinum toxin A on trigeminal neuralgia: a follow-up retrospective study of 152 patients. Exp Ther Med. 2019;18(5):3375–82. https://doi.org/10.3892/etm.2019.7988. Epub 2019 Sep 9. PMID: 31602211; PMCID: PMC6777303
86. Yoshida K. Sphenopalatine ganglion block with botulinum neurotoxin for treating trigeminal neuralgia using CAD/CAM-derived injection guide. J Oral Facial Pain Headache. 2020;34(2):135–40. https://doi.org/10.11607/ofph.2510. Epub 2019 Sep 27. PMID: 31560737
87. Piovesan EJ, Teive HG, Kowacs PA, Della Coletta MV, Werneck LC, Silberstein SD. An open study of botulinum-A toxin treatment of trigeminal neuralgia. Neurology. 2005;65(8):1306–8. https://doi.org/10.1212/01.wnl.0000180940.98815.74. PMID: 16247065
88. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes -an evidence based review. Toxicon. 2018;147:120–8. https://doi.org/10.1016/j.toxicon.2018.01.017. Epub 2018 Feb 1. PMID: 29409817
89. Hecke O, Austin SK, Khan RA, et al. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2013;155(4):654–62.
90. Schutzer-Weissmann J, Farquhar-Smith P. Post-herpetic neuralgia – a review of current management and future directions. Expert Opin Pharmacother. 2017;18(16):1739–50. https://doi.org/10.1080/14656566.2017.1392508. Epub 2017 Oct 26. PMID: 29025327
91. Benoliel R, Teich S, Eliav E. Painful traumatic trigeminal neuropathy. Oral Maxillofac Surg Clin North Am. 2016;28(3):371–80. https://doi.org/10.1016/j.coms.2016.03.002. Erratum in: Oral Maxillofac Surg Clin North Am. 2016;28(4):xi. Rafael B [corrected to Benoliel R], Sorin T[corrected to Teich S], Eli E [corrected to Eliav E]. PMID: 27475512
92. Meewis J, Renton T, Jacobs R, Politis C, Van der Cruyssen F. Post-traumatic trigeminal neuropathy: correlation between objective and subjective assessments and a prediction model for neurosensory recovery. J Headache Pain. 2021;22(1):44. https://doi.org/10.1186/s10194-021-01261-3. PMID: 34030632; PMCID: PMC8146662

93. Shinoda M, Imamura Y, Hayashi Y, Noma N, Okada-Ogawa A, Hitomi S, Iwata K. Orofacial neuropathic pain-basic research and their clinical relevancies. Front Mol Neurosci. 2021;14:691396. https://doi.org/10.3389/fnmol.2021.691396. PMID: 34295221; PMCID: PMC8291146
94. Wan CF, Song T. Comparison of two different pulsed radiofrequency modes for prevention of Postherpetic neuralgia in elderly patients with acute/subacute trigeminal herpes zoster. Neuromodulation. 2021; https://doi.org/10.1111/ner.13457. Epub ahead of print. PMID: 34008278
95. Slavin KV. Peripheral nerve stimulation for neuropathic pain. Neurotherapeutics. 2008;5(1):100–6. https://doi.org/10.1016/j.nurt.2007.11.005. PMID: 18164488; PMCID: PMC5084131
96. Li D, Xiao L. Combining botulinum toxin (A) injection with peripheral nerve stimulation in a patient for intractable ophthalmic postherpetic neuralgia. Neuromodulation. 2015;18(8):769–71. https://doi.org/10.1111/ner.12311. Epub 2015 Jun 1. PMID: 26033071
97. Rehm S, Groβkopf M, Kabelitz M, Keller T, Freynhagen R, Tölle TR, Baron R. Sensory symptom profiles differ between trigeminal and thoracolumbar postherpetic neuralgia. Pain Rep. 2018;3(1):e636. https://doi.org/10.1097/PR9.0000000000000636. PMID: 29430564; PMCID: PMC5802323
98. 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(12):1827–33. https://doi.org/10.1111/j.1526-4637.2010.01003.x. PMID: 21134121
99. Jain P, Jain M, Jain S. Subcutaneous injection of botulinum toxin in patients with post herpetic neuralgia. A preliminary study. J Assoc Physicians India. 2018;66(7):48–9. PMID: 31325262
100. Dhikav V, Anand KS, Sethi M, Verma G. Effectiveness of intradermal botulinum toxin in intractable postherpetic neuralgia. Innoriginal Int J Sci. 2016;3(5):4–6.
101. Moreau N, Dieb W, Descroix V, Svensson P, Ernberg M, Boucher Y. Topical review: potential use of botulinum toxin in the management of painful posttraumatic trigeminal neuropathy. J Oral Facial Pain Headache. 2017;31(1):7–18. https://doi.org/10.11607/ofph.1753. PMID: 28118416
102. Headache classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211. https://doi.org/10.1177/0333102417738202. PMID: 29368949
103. Yoon SH, Merrill RL, Choi JH, Kim ST. Use of botulinum toxin type A injection for neuropathic pain after trigeminal nerve injury. Pain Med. 2010;11(4):630–2. https://doi.org/10.1111/j.1526-4637.2010.00801.x. Epub 2010 Mar 4. PMID: 20210871
104. Cuadrado ML, García-Moreno H, Arias JA, Pareja JA. Botulinum neurotoxin Type-A for the treatment of atypical odontalgia. Pain Med. 2016;17(9):1717–21. https://doi.org/10.1093/pm/pnw040. Epub 2016 Apr 12. PMID: 27073225
105. Herrero Babiloni A, Kapos FP, Nixdorf DR. Intraoral administration of botulinum toxin for trigeminal neuropathic pain. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121(6):e148–53. https://doi.org/10.1016/j.oooo.2016.03.013. Epub 2016 Mar 23. PMID: 27181448
106. De la Torre Canales G, Poluha RL, Ferreira DM, Stuginski-Barbosa J, Conti PC. Botulinum toxin-A injections as therapy for chronic painful post-traumatic trigeminal neuropathy: case report. Braz Dent Sci. 2020;23(1):5-p. https://doi.org/10.14295/bds.2020.v23i1.1800
107. Borges RD, Kraychete DC, Borges EL, Melo VM. Persistent idiopathic facial pain, a diagnosis and treatment of challenge. Case report. BrJP. 2018;1:279–82. https://doi.org/10.5935/2595-0118.20180053.
108. Kim SY, Kim YK, Yun PY, Bae JH. Treatment of non-odontogenic orofacial pain using botulinum toxin-A: a retrospective case series study. Maxillofac Plast Reconstr Surg. 2018;40(1):21. https://doi.org/10.1186/s40902-018-0159-z. PMID: 30206537; PMCID: PMC6093826

109. Moreno-Hay I, Mishra P, Okeson JP. Intraoral administration of botulinum toxin for continuous dentoalveolar neuropathic pain: a case series. J Oral Facial Pain Headache. 2019;33(2):160–4. https://doi.org/10.11607/ofph.2031. Epub 2019 Feb 6. PMID: 30726860
110. García-Sáez R, Gutiérrez-Viedma Á, González-García N, Gómez-Mayordomo V, Porta-Etessam J, Cuadrado ML. OnabotulinumtoxinA injections for atypical odontalgia: an open-label study on nine patients. J Pain Res. 2018;11:1583–8. https://doi.org/10.2147/JPR.S169701. PMID: 30197533; PMCID: PMC6112804
111. McCarthy PJ, McClanahan S, Hodges J, Bowles WR. Frequency of localization of the painful tooth by patients presenting for an endodontic emergency. J Endod. 2010;36(5):801–5. https://doi.org/10.1016/j.joen.2009.12.035. Epub 2010 Mar 29. PMID: 20416423
112. Kaji K, Shinoda M, Honda K, Unno S, Shimizu N, Iwata K. Connexin 43 contributes to ectopic orofacial pain following inferior alveolar nerve injury. Mol Pain. 2016;12:1744806916633704. https://doi.org/10.1177/1744806916633704. PMID: 27030716; PMCID: PMC4955997
113. Gerwin R. Chronic facial pain: trigeminal neuralgia, persistent idiopathic facial pain, and myofascial pain syndrome-an evidence-based narrative review and etiological hypothesis. Int J Environ Res Public Health. 2020;17(19):7012. https://doi.org/10.3390/ijerph17197012. PMID: 32992770; PMCID: PMC7579138
114. Wu S, Zhang W, Yan J, Noma N, Young A, Yan Z. Worldwide prevalence estimates of burning mouth syndrome: a systematic review and meta-analysis. Oral Dis. 2021; https://doi.org/10.1111/odi.13868. Epub ahead of print. PMID: 33818878
115. Chmieliauskaite M, Stelson EA, Epstein JB, Klasser GD, Farag A, Carey B, Albuquerque R, Mejia L, Ariyawardana A, Nasri-Heir C, Sardella A, Carlson C, Miller CS. Consensus agreement to rename burning mouth syndrome and improve International Classification of Diseases-11 disease criteria: an international Delphi study. Pain. 2021;162(10):2548–57. https://doi.org/10.1097/j.pain.0000000000002243. PMID: 34534179; PMCID: PMC8449012
116. Currie CC, Ohrbach R, De Leeuw R, Forssell H, Imamura Y, Jääskeläinen SK, Koutris M, Nasri-Heir C, Huann T, Renton T, Svensson P, Durham J. Developing a research diagnostic criteria for burning mouth syndrome: results from an international Delphi process. J Oral Rehabil. 2021;48(3):308–31. https://doi.org/10.1111/joor.13123. Epub 2020 Nov 19. PMID: 33155292
117. Carreño-Hernández I, Cassol-Spanemberg J, Rodríguez de Rivera-Campillo E, Estrugo-Devesa A, López-López J. Is burning mouth syndrome a neuropathic pain disorder? A systematic review. J Oral Facial Pain Headache. 2021;35(3):218–29. https://doi.org/10.11607/ofph.2861. PMID: 34609380
118. Seo MW. Tardive tongue dyskinesia and burning mouth syndrome treated with botulinum toxin A: case report. Reactions. 2009;1258:27.
119. Restivo DA, Lauria G, Marchese-Ragona R, Vigneri R. Botulinum toxin for burning mouth syndrome. Ann Intern Med. 2017;166(10):762–3. https://doi.org/10.7326/L16-0451. Epub 2017 Apr 11. PMID: 28395302
120. Kwon DK, Park HK. Effect of botulinum toxin injection and physical therapy to reduce tongue pain and discomfort. J Oral Med Pain. 2020;45(4):120–3. https://doi.org/10.14476/jomp.2020.45.4.120.
121. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med. 2003;14(4):275–91. https://doi.org/10.1177/154411130301400405. PMID: 12907696
122. de Siqueira SR, Teixeira MJ, de Siqueira JT. Orofacial pain and sensory characteristics of chronic patients compared with controls. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;115(6):e37–45. https://doi.org/10.1016/j.oooo.2013.02.014. Epub 2013 May 1. PMID: 23643321
123. Yoon AH, Ryu JW. Masticatory muscle tenderness in burning mouth syndrome: a case control study. Oral Biol Res. 2019;43(1):83–7. https://doi.org/10.21851/obr.43.01.201903.83.
124. Drinovac Vlah V, Bach-Rojecky L. What have we learned about antinociceptive effect of botulinum toxin type A from mirror-image pain models? Toxicon. 2020;185:164–73. https://doi.org/10.1016/j.toxicon.2020.07.014. Epub 2020 Jul 19. PMID: 32698026

Chapter 17
Botulinum Neurotoxin Treatment of Unusual and Rare Painful Disorders

Introduction

Some rare and uncommon neurological disorders are associated with significant amount of local pain. The spectrum of neurological symptoms in these rare disorders is wide including increased muscle tone, involuntary movements, and abnormal postures. The pain associated with these conditions often responds partially to conventional analgesic medications, and most patients are not happy with their level of pain control.

This chapter focuses on the effect of BoNTs on alleviation of the pain associated with uncommon and rare disorders. Four such disorders are selected for discussion in this chapter: stiff-person syndrome, painful legs-moving toes, painful camptocormia, and the syndrome of central pain. Some case reports are presented from the author's experience to illustrate the patients' clinical features, recommended toxin doses, and the appropriate injection techniques.

Stiff-Person Syndrome (SPS)

Stiff-person syndrome (previously called stiff-man syndrome or the syndrome of Moersch and Woltman) is an autoimmune disorder characterized by progressive increase in muscle tone (rigidity), associated with painful, trigger-induced muscle spasms, predominantly affecting axial and proximal limb muscles [1]. The exact pathophysiology of SPS is not known, but the presence of antibodies against GABA decarboxylase (GAD), the rate-limiting enzyme which makes GABA, suggests an inherent dysfunction of inhibitory spinal cord mechanisms [2]. Increased levels of GAD-65 antibody are found in 60–80% of the patients with SPS. The level of anti-GAD antibody may not correlate with the severity of symptoms in SPS [1],

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_17

however. Approximately 30% of the patients with SPS have type 1 diabetes with autoantibodies to the same isoform of GAD65 shared by both disorders [3]. Electromyography shows continuous muscle activity and firing of motor unit potentials which are easily triggered by photic or acoustic stimuli. This increased activity is seen in both agonist and antagonist muscles, and unlike a normal muscle, volitional activation of the agonist muscles does not reduce or stop the activity of the antagonist muscles [4].

Based on their experience at Mayo Clinic, McKeon et al. [5] defined SPS as a rare disorder as they observed only an average of four new patients per year. Of 99 patients that they diagnosed over 25 years, 67 were female (68%), and 89 were Caucasian (91%). They subdivided the clinical picture of SPS into classic SPS (65 patients) with predominantly lower trunk involvement conforming to the original description of Moersch and Woltman [6] and a partial variant (31 patients) with involvement of one or more (usually lower) limbs. This variant is also called stiff-limb syndrome (SLS) by others in the field. Included among the 99 patients were three patients with the poorly understood disorder of progressive encephalomyelitis and rigidity (PERM). Eighteen of 99 patients (10.6%) were seronegative for anti-GAD antibody. Seronegativity was more common among patients with the partial variant of SPS (12 out of 31 versus 6 out of 65, $P < 0.05$). Some patients with stiff-person syndrome demonstrate significant myoclonus for whom the term jerky stiff-person syndrome is used.

SPS is occasionally a manifestation of an occult neoplasm. Paraneoplastic SPS accounts for 5% of SPS patients and has been described in association with carcinoma of the breast, lung, colon, thymus, and lymphoma [7]. The SPS symptoms may precede detection of the neoplasm by months or even years. Presence of anti-amphiphysin antibodies in these patients correlates with adenocarcinoma of the breast or small cell carcinoma of the lung [8, 9]. Maurinson and Guarnacia [10] emphasized epidemiological and clinical features of SPS with amphiphysin antibodies; these features include older age, marked predominance among women, absence of diabetes, and cervico-brachial rigidity. Increased level of anticardiolipin antibody and beta-2 glycoprotein 1 has been reported in SPS [11].

Treatment of SPS is aimed at reducing muscle tone, alleviating pain, and preventing further damage to the central nervous system (CNS). High doses of diazepam (40–100 mg daily) are commonly used for reducing muscle stiffness in SPS. Reduction of muscle tone can be achieved also by baclofen (including the use of intrathecal route), tizanidine, or dantrolene. Levetiracetam, vigabatrin, valproic acid, clonazepam, and gabapentin are used to reduce CNS hyperexcitability. Anecdotal observations claim improvement of SPS symptoms with short courses of steroids [12]. Intravenous immunoglobulin (IVIG) therapy is often employed to prevent further damage to the CNS. The recommended total dose is 2 gram/kg, over 3–5 days and may be repeated every 4–6 weeks [13]. A recent study has shown the continued efficacy of this treatment over 5 years [14].

More severe cases, and especially those with compromised respiratory function due to severe spasms of the thoracic muscles, may require plasma exchange (PE). Czempik et al. [15], in a recent review of literature, noted marked improvement of

symptoms after plasmapheresis in 70% of patients with SPS and high anti-GAD 65 antibody titers. In some patients, after treatment, anti-GAD65 titers did not show appreciable reduction despite notable clinical improvement. Although a controlled study showed no advantage for rituximab over other modes of therapy in SPS [16], case reports claim its effectiveness against SPS symptoms [17, 18]. Recently, a group of investigators reported gluten sensitivity in patients with SPS and stated some patients with SPS improve with gluten-free diet [19].

Pain is a common complaint in patients with stiff-person syndrome. In the classic form of SPS, rigidity of lumbar and lower thoracic, abdominal, or paraspinal muscles is often associated with lumbar lordosis and deep pain [20]. Paroxysmal local pain in the form of muscle spasms is also common in trunk and thigh muscles. Some patients with partial SPS and lower limb involvement manifest neuropathic pain with a significant burning quality (personal observations).

BoNT Treatment of Pain in Stiff-Person Syndrome

Davis and Jabbari [21, 22] were the first to report marked improvement of low back pain and reduction of paraspinal rigidity in SPS after injection of onabotulinumtoxinA into paraspinal ad hamstring muscles of a 36-year-old African American gentleman who had developed progressive stiffness of the thighs, lower abdominal, and back muscles over an 18 month period (Case 17.1). Initially, his problems were attributed to lumbar osteoarthritis, and he was treated with non-steroidal, anti-inflammatory agents. However, he gradually developed lumbar lordosis and severe, painful muscle spasms in the thigh, back, and abdominal muscles. These spasms were easily triggered by physical activity. A sister had non-insulin-dependent diabetes and hypothyroidism, but the patient's past medical history was otherwise normal. On examination, pertinent physical findings were lumbar lordosis, markedly increased tone in the thigh, abdominal, and low back muscles bilaterally, inability to change position from supine to standing position unassisted and an awkward, hesitant, and short stepped gait. In addition, he had diffuse hyperhidrosis. An extensive laboratory workup including muscle biopsy of the right thigh muscles and cerebrospinal fluid values was normal with the exception of electromyography (EMG) and the level of anti-GAD antibodies. On EMG, the involved muscles showed continuous motor unit firing at rest in both the agonist and antagonist muscles. Serum GAD antibody was positive at a high dilution of 1/122,000, while the CSF anti-GAD level was 1/128 (normal values from Mayo clinic are <1/120 and <1/2, respectively). Treatment with a combination of baclofen and diazepam partially improved muscle rigidity. Patient was injected with 550 units of onabotulinumtoxinA into erector spinae and thigh muscles. Erector spinae was injected at the lumbar region, 40 units per each of five lumbar level bilaterally (200 units on each side) (Fig. 17.1a). Each hamstring muscle received 75 units of the toxin—25 units per each of three sites—(Fig. 17.1b). Within a week, the patient reported cessation of muscle spasms and significant improvement of back and thigh rigidity. A repeat injection, 6 months

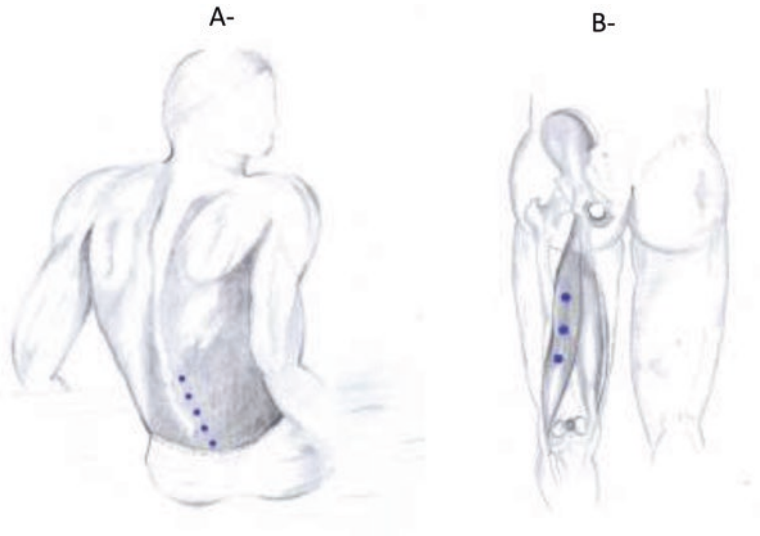

Fig. 17.1 (**a**, **b**) (Case 1): SPS with severe bilateral paraspinal rigidity. (**a**) Sites of injections into lumbar erector spinae at five lumbar levels (one side is shown). (**b**) Injection into hamstring at three sites. Drawings courtesy of Shahroo Etemad-Moghadam, DDS

later, produced similar effects. There were no side effects. In particular, no weakness was noted in the lower limbs, and the patient did not report any problems with balance and ambulation.

In 1997, Liguori et al. [23] described the results of the BoNT-A (aboA) injection into affected muscles of two patients with stiff-person syndrome. Both patients were women with the partial variant (stiff-limb syndrome) of SPS. Both patients had detectable serum anti-GAD antibodies, but the exact level was not mentioned. In one patient, a total of 700 units of abobotulinum toxinA (aboA) was injected into different muscles of one thigh. The second patient received a total of 1000 units of aboA injected into upper limb muscles (deltoid, biceps, brachioradialis). The outcome for rigidity was assessed blindly at baseline and following injections using the Unified Parkinson's Disease Rating Scale (UPDRS). The spasms were evaluated on a scale of 1–5 (5 being 30 or more spasms per day). Treatment with abobotulinumtoxin A reduced both pain and rigidity for up to 7 months, and repeat injections were also successful over a follow-up period of 2 years.

Anagnustou and Zambelis [24] reported the case of a 40-year-old gentleman with a history of left leg stiffness for 9 years. The patient gradually developed painful knee extension spasms. Treatment with diazepam was partially helpful. Serum anti-GAD antibody level was 500 units/ml (normal <5/ml). Injection of 900 units of abobotulinum toxin A into the left leg muscles (350 units into vastus lateralis, 350 units into vastus medialis, 200 units into rectus femoris) eliminated the painful extension spasms of the leg and reduced the muscle tone (Ashworth scale: 4, before injection; 1, 4 weeks after injection). In this patient with stiff-limb syndrome,

previous injections of aboA with doses smaller than 900 units had resulted in either no or only modest improvement.

A 48-year-old male with SPS who experienced facial and neck muscle spasms uncontrolled by polypharmacotherapy—including even intrathecal baclofen pump–demonstrated significant relief of pain and spasms after bilateral injection of botulinum toxin A into the masseter and neck paraspinal muscles [25]. The injected dose was 50–75 units into masseters, 75–100 units into trapezius, and 300 units into paraspinal neck muscles. Another two brief case reports also reported that intramuscular injection of BoNT-A can benefit patients with stiff-person syndrome [26, 27] (Table 17.1).

Case 17.1 (Limb Variant of SPS)
A 44-year-old male patient was referred to the Yale Movement Disorder Clinic for evaluation of "muscle pain and muscles stiffness." His symptoms had begun 3 years earlier with increased daily fatigue and low motivation for engaging in physical activity. He was told by a physician to keep well hydrated and consume potassium-rich foods. Subsequently, the patient developed a chronic sensation of "tightness/stiffness" in his lower limbs and severe episodic cramping of muscles in his thighs, calves, toes, and flanks as well as his jaw muscles. Intermittent cramping and pain in the jaw muscles made speaking difficult. The more severe episodes lasted 30 min but only occurred after physical exertion, about five times per week. The patient

Table 17.1 Botulinum toxin treatment in stiff-person syndrome—cases reported in English language

Authors	Number of cases	Type of botulinum toxin	Muscles injected	Dose in units
Davis and Jabbari [21]	1	OnabotulinumtoxinA	Paraspinal (erector spinae)	40–50/lumbar level
Liguori et al. [23]	Case 1 Case 2	OnabotulinumtoxinA OnabotulinumtoxinA	Hip adductors Biceps femoris Tibialis posterior Soleus Trapezius Deltoid Biceps brachii	50–100 50–300
Anagnostou and Zambelis [24]	1	AbobotolinumtoxinA	Vastus lateralis Vastus medialis Rectus femoris	100–350
Pakeerappa et al. [25]	1	OnabotulinumtoxinA	Bilateral masseters Trapezius Neck paraspinal muscles	50–75 75–100 300
Esplin et al. [26]	1	IncobotulinumtoxinA	Biceps brachii Brachioradialis Flexor digitorum sf. and pf.	Total: 300
Zhang et al. [28]	1	Botulinum toxin A	Lower limbs	Not mentioned

also reported continuous twitching of his right quadriceps, intermittent twitching of his left quadriceps, and bilateral calf muscles. He had also noticed involuntary jerking of his limbs during the day and night. The patient felt his right thigh has grown larger in the last year and had noticed increased hair growth on his right upper thigh extending to the gluteus region. Diazepam, 10 mg twice daily and Percocet 325 mg, two to three times daily, offered only modest relief of the symptoms.

Neurological examination demonstrated normal cognition, speech, intact cranial nerves, and cerebellar and sensory functions. There was increased muscle tone in the right thigh (Ashworth score of 3) and lower abdominal muscles. Painful muscle twitches could be provoked easily in the right thigh muscles by passive and active stretch or pressing the right foot on the floor. The rest of the neurological examination was normal. Electromyography showed continuous muscle activity at rest in the right vastus medialis and rectus femoris muscles (Videotape 16-1). The serum anti-GAD antibody level was 3 (normal, <0.5), significantly elevated from 0.07 obtained a year earlier. Serum levels of glucose; total CK l, HgA1c, and TSH; insulin autoantibody (<5.0); and striatal and acetylcholine receptor antibodies as well as the paraneoplastic panel which included anti-amphiphysin antibody were all normal. Magnetic resonance imaging of the spine showed moderate cervical arthritic changes.

The patient was treated with intravenous immunoglobulin (IVIG), 2 gram/kg given over a period of 3–5 days at 4 week intervals. This treatment improved the muscle rigidity after 3 months, but the effect on painful muscle spasms was modest. The patient then received an intramuscular injection of 400 units of botulinum toxin A (onaA) into the right thigh muscles. A total of 100 units was injected at two sites (50 units/site) into each of the following four muscles: vastus medialis, rectus femoris, vastus lateralis, and hamstring. After 2 weeks, patient reported reduction in frequency and intensity of muscle cramps in the right vastus lateralis and rectus femoris muscles. However, the spasms of gastrocnemius muscles responded less favorably.

Comment

Since the original description of SPS (initially called stiff-man syndrome) [6], the clinical spectrum of SPS has been expanded to include several atypical variants [28, 29]. Although increased anti-GAD antibodies are considered a hallmark of SPS, the antibody spectrum associated with SPS has also been broadened to include antibodies against dipeptidyl-peptidase-like protein-6 (DPPX), gamma-aminobutyric acid type A receptor (GABAAR), glycine receptor (GlyR), and glycine transporter 2 (GlyT2) [30].

Pain is a major symptom in many patients with SPS. The observations listed above demonstrate that both onaA and aboA injections into rigid and painful muscles can alleviate pain in patients with SPS and improve patients' quality of life. An important caveat of BoNT treatment in SPS is sufficiency of the injected dose. The involved muscles are large muscles, and therefore, it is easy to underestimate the

Table 17.2 Author's recommended dose of onabotulinumtoxinA for severe limb rigidity in stiff-person syndrome

Muscles of upper limb	Botulinum toxin dose-in units	Muscles of lower limb	Botulinum toxin dose-in units
Biceps brachii	50–150	Hamstring	100–200
Triceps brachii	50–150	Rectus femoris	100–200
Brachioradialis	50–100	Gastrocnemius	100–200
Deltoideus	50–100	Soleus	50–100
Trapezius	150–200	Tibialis posterior	50–150
Levator scapulae	50–100	Tibialis anterior	50–150

required dose for the patient. For patients with bilateral low back rigid muscles, I recommend a total dose of 400 units of onA. This can be given at five lumbar levels into erector spinae, 40 units/level for a total of 200 units on each side. A comparable dose of aboA would be roughly 500 units for each side (using 1:2.5 ratio between ona and abo toxins). The recommended dose for stiff-limb muscles is shown in Table 17.2. It is important to remember that BoNT treatment is only for symptomatic relief and not a substitute for modulation of the immune system, which is often needed in these patients. Verification of efficacy of BoNT treatment in SPS requires data from randomized, placebo-controlled studies. Such studies are difficult to perform in a sizable cohort of patients with SPS due to the rarity of this disorder (1–2/million population) [31].

Pain improvement after injection of BoNTs in SPS most likely involves different mechanisms including relaxation of tight muscles due to blocking of acetylcholine release and via peripheral as well as central analgesic effects of botulinum neurotoxins through its inhibiting effects upon pain transmitters [32–54].

The Syndrome of Painful Legs-Moving Toes

This syndrome was first described by Spillane et al. [55] in 1971 in six patients who presented with involuntary toe or foot movements associated with pain in the toes, feet, or leg. The pain often preceded the involuntary movements and has been described as aching, burning, jabbing, or throbbing. Involuntary movements were often slow and writhing with a flexion–extension of the toes or foot. Subsequently, a number of less common variants of this syndrome were described and designated as painful hand-moving fingers, painless moving toes, and painless moving fingers. The movements in PLMT can start in one limb and gradually progress to the other limb or move from a lower limb to the upper limb [56, 57]. The syndrome is rare with only 14 cases observed among 4780 patients referred to Mayo Clinic for evaluation of movement disorders over a 10-year period [58].

Nathan [59] and Schott [60] proposed that PLMT results from injury to the peripheral nervous system (nerves, plexus, roots), citing several examples of this

association. Support for this view has emerged from cases of cervical and lumbar spine disease that have improved after surgical intervention. Miyakawa et al. [61] reported a patient with painful arm-moving fingers with cervical spondylosis at C5-C6 level in whom foraminectomy stopped both the finger movements and the arm pain. Their second patient had developed leg pain and toe movements (PLMT) 2 weeks after L5-S1 discectomy. The pain and movements disappeared after lumbar nerve blocks. Others have also reported various levels of pain relief following lumbar epidural block or spinal cord stimulation [62, 63].

In the largest series of patients reported to date with this syndrome, Dressler et al. [64] noted a variable age of onset in adults (youngest, 28 years of age) and a predominance among women (14 out of 20). Also, a majority of their patients had peripheral nervous system injury. Due to bilateral symptom distribution in some patients, the authors proposed the existence of a central generator for the movements which presumably develops following a cascade of events after the peripheral injury. Presence of a "central oscillator" above the spinal cord level has been strongly suggested from transcortical magnetic stimulation of the left motor cortex which has demonstrated failure of cortical facilitation in a patient with bilateral finger movements and painful hands. A detailed electrophysiological assessment of this case showed no abnormality of spinal inhibitory mechanisms [65]. In another patient with bilateral finger movements, presence of out of phase discharges in the involved hand muscles suggested existence of two independent central generators [56]. In a recent study, single-photon emission computed tomography (SPECT) of the brain demonstrated hyperperfusion of the anterior cingulate gyrus, as well as primary and secondary sensory cortices considered to be parts of the brain's pain matrix in PLMT syndrome [66].

In the series reported from Mayo Clinic, 11 of 14 patients also had electrophysiological evidence of peripheral nervous system dysfunction and were affected by a variety of neuropathies caused by diabetes, vitamin deficiencies, lupus, and Sjogren syndrome [58]. In most affected patients, electromyography (EMG) demonstrated rhythmic, 1–3 HZ discharges with duration of each discharge ranging from 0.5 to 2 seconds. In several patients, the pattern of EMG discharge resembled that of myokymia.

Treatment of patients with PLMT is challenging and was called "notoriously difficult" by Dressler et al. [64]. In the Mayo Clinic series that was published 12 years later, Alvarez et al. [58] treated most patients with gabapentin and pregabalin and reported partial pain relief. Low dose clonazepam and dopaminergic therapy have helped some patients [67, 68]. Recalcitrant pain in PLMT may require treatment with opioids. In an extensive review, Reich described in detail clinical and therapeutic options for painful legs-moving toes syndrome [69].

BoNT Treatment of Painful Legs-Moving Toes (PLMT) Syndrome

Small case series and individual case reports suggest efficacy of botulinum toxin injection in alleviating the symptoms (including pain) of PLMT. In collaboration with Dr.Carlos Singer's group at the University of Miami, we described significant reduction of pain and movements in two patients with PLMT syndrome after injection of onaA into the affected muscles [57]. One of the patients, a 62-year-old gentleman, complained of low back pain for a year followed by development of pain in both calves and feet associated with involuntary flexion–extension of the toes bilaterally. OnabotulinumtoxinA was injected into the following muscles bilaterally: gastrocnemius (50 units, each side), flexor digitorum brevis (45 units, each side), and lower lumbar paraspinal muscles (60 units on each side). The second patient, a 72-year-old female, also had bilateral PLMT with irregular toe movements and pain in the feet. Injection of 25 units of onaA into flexor digitorum brevis of each foot relieved pain and slowed down the movements.

Schoffer [70] described a 17-year-old boy who developed burning sensation and cramps in the calf and writhing involuntary movements of the fourth and fifth toes a year after a hamstring injury. Injection of 20 units of onabotulinumtoxinA into the abductor digiti minimi and 10 units into flexor digiti minimi eliminated the movements and the calf pain.

Rodriguez and Fernandez [71] described a 43-year-old man who developed adduction-abduction movements of the right big toe and, to a lesser extent, other toes with significant foot and lower leg pain. Injection of onabotulinumtoxinA (onaA) under electromyographic guidance into the foot muscles stopped the movements and significantly reduced the pain intensity. The dose was as follows: 25 units in the flexor hallucis brevis, 25 units in adductor hallucis, and 50 units in the flexor digitorum brevis. A long-term follow-up of 3 years showed continued efficacy of treatment with onaA injections every 3 months.

Bosco et al. [72] described a 56-year-old man with a history of frequent movements of the right toes and pain (pulling/burning) radiating from the toes to the anterolateral part of the leg and thigh. Treatments with pregabaline, clonazepam, duloxetine, and trazodone did not alleviate the pain. Injection of incobotulinumtoxinA (Zeomin) into foot muscles (Fig. 17.2) resulted in complete suppression of the movements and remarkable pain relief (pre-injection VAS:8/10, post-injection 0/10).

Comment

Painful leg-moving toes syndrome is a rare disorder but can be a cause of significant pain and discomfort for the patients. The observations cited above suggest the efficacy of local injections of BoNT-A (Botox or Xeomin) in management of the pain

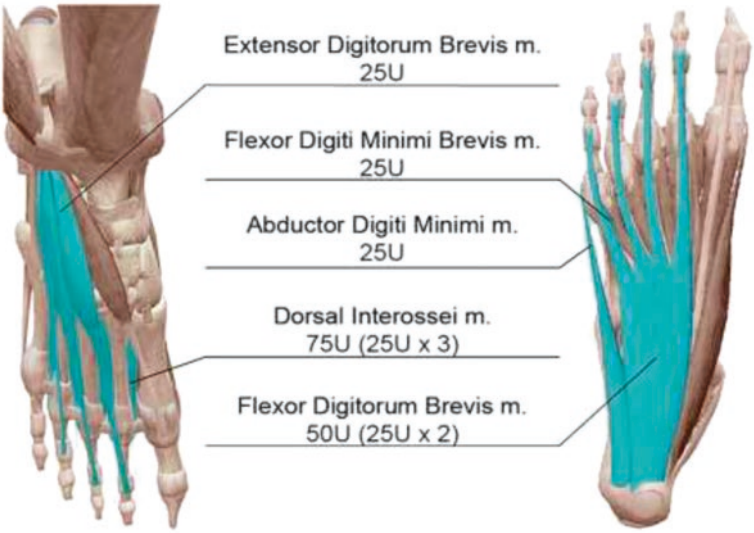

Fig. 17.2 Effective dose of incobotulinumtoxinA(Xeomin) and injected muscles, in a patient with PLMT- From Bosco et al. J Neurology 2020 [72]. Reproduced with permission from the publisher (Springer)

and movements in patients with this syndrome. The mechanism of pain relief in PLMT, as described earlier for SPS, probably involves both suppression of muscle spasms via inhibition of acetylcholine release from neuromuscular junction and direct inhibitory effect of BoNTs upon pain transmitters at peripheral and central levels. The technique of injection needs to be individualized according to the patient's symptomatology. With experience, refinement of injection techniques can lead to better results.

Camptocormia

Camptocormia is an abnormality of posture characterized by marked thoracolumbar flexion which manifests during standing and walking and abates in the position of repose. A forward flexion of greater than 45° with resolution upon assuming a supine posture is considered diagnostic for camptocormia. The word camptocormia is derived from two Greek words kamptos, which means bent forward, and kormos, meaning torso. In medicine, the term camptocormia was coined in 1915 to describe the posture in shell-shocked soldiers who fought in trenches during World War I [73]. The author had suspected a psychogenic cause for war-related camptocormia. However, almost a century earlier, another neurologist had used the term "bent spine" to describe the posture of a Spanish painter in 1818 [74]. It is now clear that most cases of camptocormia are not psychogenic and camptocormia can be

caused by a large number of pathologic conditions [75–77]. Typical camptocormia is usually seen in association with neurodegenerative disorders, especially Parkinson's disease (PD), and multiple system atrophy (MSA) [78–81], myopathies of posterior trunk muscles and spine disease. Other common causes include drug-induced camptocormia, spine and disc disease, and even certain neuropathies. Acute camptocormia has been described also as a manifestation of tetanus [82]. Camptocormia associated with Parkinson's disease or multiple system atrophy seems to be related to basal ganglia dysfunction, a view which is supported by significant improvement of camptocormia in some patients after bilateral pallidal or bilateral subthalamic deep brain stimulation [83, 84]. Margraf et al. [85], however, hold the view that camptocormia in PD is a myopathy of paraspinal muscles. In their study of 15 patients with PD and camptocormia, both electromyography and muscle biopsy demonstrated a pattern of myopathy. Camptocormia has been described in patients affected by genetic abnormalities such as mutation of POLG gene that encodes the catalytic subunit of DNA polymerase gamma and is responsible for replication of the mitochondrial genome [86]. Camptocormia has also been reported in a case of biopsy-proven inclusion body myositis (proved by biopsy) as an isolated symptom [87].

Treatment of camptocormia is difficult. Pharmacological treatment is not usually effective. Anecdotal reports indicate that some patients may respond to dopaminergic drugs [85, 88]. Improvement of camptocormia has been reported after transcranial magnetic stimulation, but the effect is transient [89]. A recent report on 17 patients with camptocormia and deep brain stimulation of globus pallidus resulted in significant improvement of symptoms in close to two thirds of the patients [90]. Most patients with camptocormia complain of intermittent back pain. Some patients demonstrate painful contractions of abdominal muscles. In some patients, pain can be the major complaint [91, 92]. In such patients, the treatment should aim to improve both posture and pain.

BoNT Treatment of Camptocormia

In recent years, several medical groups have reported on the effects of BoNT injections into abdominal and ileopsoas muscles of patients with camptocormia. Azher and Jankovic [77] treated nine patients with camptocormia with onabotulinumtoxinA injections into rectus abdominis muscles. The patients had clinical evidence of contractions of rectus abdominis muscles. The injected dose per session was 300–600 units. Four of nine patients demonstrated notable improvement of their posture. In another study [93], the authors investigated the effect of botulinum toxin injection in a 66-year-old patient with camptocormia and painful abdominal wall contractions. Injection of 200 units of onabotulinumtoxinA into each rectus abdominis and each external abdominal oblique muscle resulted in marked improvement of posture and reduction of painful muscle contractions.

In contrast, van Coelln et al. [94] reported no improvement of camptocormia after BoNT injection in four patients with PD and MSA. Abobotulinum toxinA was injected, 500 units per side, into the deep ileopsoas muscle under ultrasound guidance. Injections were repeated every 4–6 months with escalating doses of 1000 and 1500 units per side. Patients' posture was monitored at baseline and every 4–6 months, and none of the four patients showed any improvement. In two other patients, ultrasound-guided injection of onabotulinumtoxinA, 100 units per each ileopsoas, also failed to improve camptocormia [95] (Colosimo and Salvatori 2009). Fietzek et al. [95] also injected BoNT-A (IncoA), 100–300 units into either iliopsoas or rectus abdominis muscles of ten patients with camptocormia. Six patients chose improvement of posture while four chose alleviation of pain as a desired outcome. At 3 weeks, no improvements were reported in either posture or pain.

Comment

Botulinum toxin treatment of camptocormia requires significant familiarity with the anatomy of abdominal muscles and expertise in electromyography. The literature on the effect of BoNT injection in camptocormia is controversial. Negative results are mostly reported when injections are primarily aimed into ileopsoas muscle. According to Dr. Jankovic at Baylor Medical College, the best results with BoNT therapy in camptocormia can be achieved in the dystonic form of this disorder and with combined injection of rectus abdominis and external oblique muscles [96]. I agree with this observation. In my experience with onabotulinumtoxinA in six patients with camptocormia, three demonstrated notable improvement with a technique which combines injection of both rectus abdominis and oblique abdominal muscles (Fig. 17.3). In one of these three patients who had painful camptocormia, onaA injections also significantly alleviated his pain (pre-injection VAS level of 7 was lowered to VAS level 2). In this patient, each rectus abdominis was injected with 200 units of onaA, and each abdominal external oblique muscle was injected with 150 units of onaA for a total of 700 units per session. No side effects were noted. Higher doses are recommended in cases of recalcitrant camptocormia by experts in BoNT therapy [96]. Despite the controversial literature, careful selection of muscles and sufficient dose of BoNT may produce quite satisfactory results in camptocormia [97].

Nontraumatic Central Pain

Reports of botulinum toxin therapy for management of central pain are scarce in the literature. The author first reported effectiveness of BoNT injections in improvement of central pain resulting from intramedullary pathology in two patients [98].

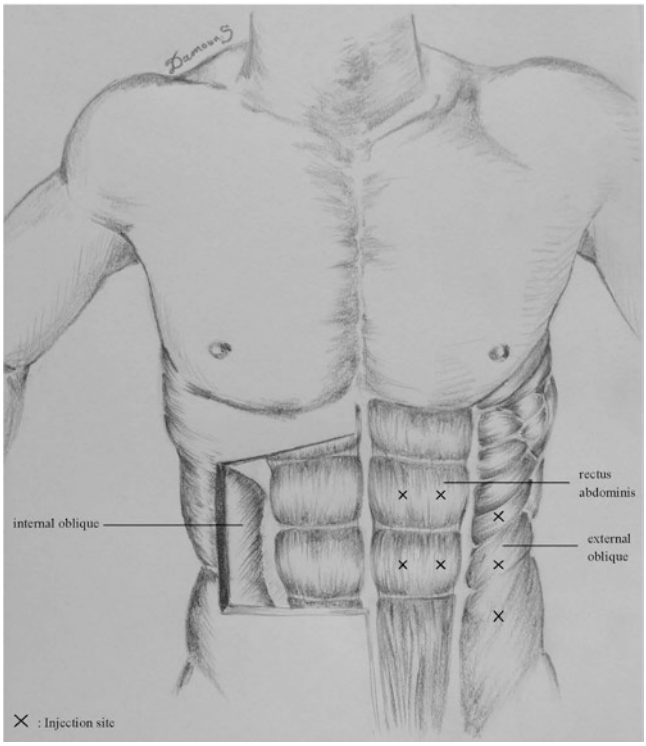

Fig. 17.3 Injection sites into rectus abdominis and external oblique in camptocormia (author's method). Drawing courtesy of Damoun Safarpour, M.D.

Case 1

A 55-year-old female asked for medical help for severe burning pain in both arms from elbow down to the wrist. On examination, the patient showed marked sensitivity to touch in T1 dermatomes bilaterally (Fig. 17.4). The symptoms began 7 years ago and intensified gradually over years. Six year ago, a computed tomography scan (CT) demonstrated an intramedullary lesion that, on surgical exploration, proved to be a intramedullary angioma. Partial resection of the lesion did not improve patient's pain**.** Treatment with a variety of analgesic medications including opioids was not helpful. On each side, the T1 dermatome was injected at 20 points subcutaneously, each receiving 5 units (100 units/side). After 1 week, the patient reported marked improvement of spontaneous pain and skin sensitivity. Over 3 years of follow-up, she chose to receive onaA injections every 4 months.

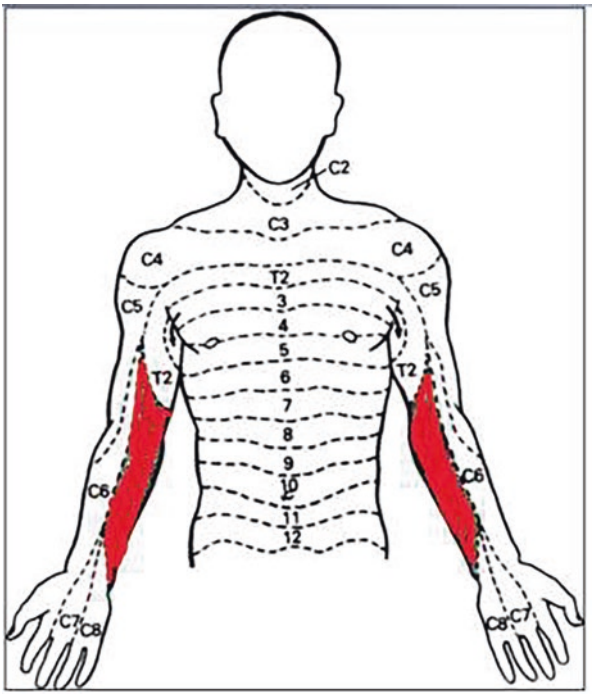

Fig. 17.4 Case 1. Areas of exquisite skin sensitivity to touch marked by red color (T1 dermatomes)

Case 2

A 33-year-old female suffered from 7 days of left-sided neck and head pain, nausea, vertigo, and right-sided weakness. An MRI demonstrated infarction of the three upper segments of spinal cord up to lower medulla. An angiogram disclosed severe spasm of the right vertebral artery. Over the following weeks, the patients developed exquisite skin sensitivity over the right posterior neck and right shoulder lesions. Touching the area brought tear to her eyes. The patient had suffered from severe bouts of migraine since age 19. As analgesic medications failed to improve her condition, she visited the Neurology Clinic at Walter Reed Army Medical Center and asked for help. Subcutaneous injection of onabotulinumtoxinA (5 units at 16 points) over the posterior neck and shoulder region improved pain and discomfort to her satisfaction. Every 3 months, injection of the same dose of onaA proved to be effective relieving her discomfort.

Park et al. [99] recently reviewed the pathophysiology of central neuropathic pain and presented the limited literature in this area in an informative table.

References

1. Ciccotto G, Blaya M, Kelley RE. Stiff person syndrome. Neurol Clin. 2013;31(1):319–28. https://doi.org/10.1016/j.ncl.2012.09.005. PMID: 23186907
2. Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med. 1990;322(22):1555–60. https://doi.org/10.1056/NEJM199005313222202. PMID: 2135382
3. Raju R, Hampe CS. Immunobiology of stiff-person syndrome. Int Rev Immunol. 2008;27(1-2):79–92. https://doi.org/10.1080/08830180701883240. PMID: 18300057
4. Rakocevic G, Floeter MK. Autoimmune stiff person syndrome and related myelopathies: understanding of electrophysiological and immunological processes. Muscle Nerve. 2012;45(5):623–34. https://doi.org/10.1002/mus.23234. PMID: 22499087; PMCID: PMC3335758
5. McKeon A, Robinson MT, McEvoy KM, Matsumoto JY, Lennon VA, Ahlskog JE, Pittock SJ. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012;69(2):230–8. https://doi.org/10.1001/archneurol.2011.991. PMID: 22332190
6. Moersch FP, Woltman HW. Progressive fluctuating muscular rigidity and spasm ("stiff-man" syndrome); report of a case and some observations in 13 other cases. Proc Staff Meet Mayo Clin. 1956;31(15):421–7. PMID: 13350379
7. Hadavi S, Noyce AJ, Leslie RD, Giovannoni G. Stiff person syndrome. Pract Neurol. 2011;11(5):272–82. https://doi.org/10.1136/practneurol-2011-000071. PMID: 21921002
8. De Camilli P, Thomas A, Cofiell R, Folli F, Lichte B, Piccolo G, Meinck HM, Austoni M, Fassetta G, Bottazzo G, Bates D, Cartlidge N, Solimena M, Kilimann MW, et al. The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of Stiff-Man syndrome with breast cancer. J Exp Med. 1993;178(6):2219–23. https://doi.org/10.1084/jem.178.6.2219. PMID: 8245793; PMCID: PMC2191289
9. Nguyen-Huu BK, Urban PP, Schreckenberger M, Dieterich M, Werhahn KJ. Antiamphiphysin-positive stiff-person syndrome associated with small cell lung cancer. Mov Disord. 2006;21(8):1285–7. https://doi.org/10.1002/mds.20910. PMID: 16671079
10. Murinson BB, Guarnaccia JB. Stiff-person syndrome with amphiphysin antibodies: distinctive features of a rare disease. Neurology. 2008;71(24):1955–8. https://doi.org/10.1212/01.wnl.0000327342.58936.e0. Epub 2008 Oct 29. PMID: 18971449; PMCID: PMC2676978
11. Tang LY, Yu SY, Huang YH. Stiff person syndrome with elevated titers of antibodies against cardiolipin and β2 glycoprotein 1: a case report and literature review. J Musculoskelet Neuronal Interact. 2018;18(3):389–92. PMID: 30179217; PMCID: PMC6146186
12. Blum P, Jankovic J. Stiff-person syndrome: an autoimmune disease. Mov Disord. 1991;6:12–20.
13. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med. 2001;345(26):1870–6. https://doi.org/10.1056/NEJMoa01167. PMID: 11756577
14. Bose S, Thompson JP, Sadalage G, Karim A, Jacob S. Quantitative assessment of response to long-term treatment with intravenous immunoglobulin in patients with stiff person syndrome. Mov Disord Clin Pract. 2021;8(6):868–74. https://doi.org/10.1002/mdc3.13261. PMID: 34401404; PMCID: PMC8354084
15. Czempik PF, Gawryluk J, Wiórek A, Krzystanek E, Krzych ŁJ. Efficacy and safety of therapeutic plasma exchange in stiff person syndrome. Open Med (Wars). 2021;16(1):526–31. https://doi.org/10.1515/med-2021-0220. PMID: 33821220; PMCID: PMC8010154
16. Dalakas MC, Rakocevic G, Dambrosia JM, Alexopoulos H, McElroy B. A double-blind, placebo-controlled study of rituximab in patients with stiff person syndrome. Ann Neurol. 2017;82(2):271–7. https://doi.org/10.1002/ana.25002. Epub 2017 Aug 9. PMID: 28749549; PMCID: PMC5755707
17. Baker MR, Das M, Isaacs J, Fawcett PR, Bates D. Treatment of stiff person syndrome with rituximab. J Neurol Neurosurg Psychiatry. 2005;76(7):999–1001. https://doi.org/10.1136/jnnp.2004.051144. PMID: 15965211; PMCID: PMC1739691

18. Fekete R, Jankovic J. Childhood stiff-person syndrome improved with rituximab. Case Rep Neurol. 2012;4(2):92–6. https://doi.org/10.1159/000339446. Epub 2012 May 31. PMID: 22740823; PMCID: PMC3383307
19. Hadjivassiliou M, Zis P, Sanders DS, Hoggard N, Sarrigiannis PG. Stiff person syndrome and gluten sensitivity. Nutrients. 2021;13(4):1373. https://doi.org/10.3390/nu13041373. PMID: 33923904; PMCID: PMC8073141
20. Bastin A, Gurmin V, Mediwake R, Gibbs J, Beynon H. Stiff man syndrome presenting with low back pain. Ann Rheum Dis. 2002;61(10):939–40. https://doi.org/10.1136/ard.61.10.939. PMID: 12228170; PMCID: PMC1753919
21. Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A. Mov Disord. 1993;8:371–3.
22. Richardson, Jabbari. Chapter 19, Treatment of stiff-person syndrome with botulinum toxin. In: Troung, Hallett, Zachary, Dressler, editors. Manual of botulinum toxin therapy. 2nd ed. Cambrige University Press; 2013. p. 168–73.
23. Liguori R, Cordivari C, Lugaresi E, Montagna P. Botulinum toxin A improves muscle spasms and rigidity in stiff-person syndrome. Mov Disord. 1997;12:1060–3.
24. Anagnostou E, Zambelis T. Botulinum toxin A in anti-GAD-positive stiff-limb syndrome. Muscle Nerve. 2012;46:457–8.
25. Pakeerappa PN, Birthi P, Salles S. Botulinum toxin a injection to facial and cervical paraspinal muscles in a patient with stiff person syndrome: a case report. PM R. 2015;7(3):326–8. https://doi.org/10.1016/j.pmrj.2014.10.013. Epub 2014 Nov 6. . PMID: 25459656
26. Esplin NE, Stelzer JW, Legare TB, Ali SK. Difficult to treat focal, stiff person syndrome of the left upper extremity. Case Rep Neurol Med. 2017;2017:2580620. https://doi.org/10.1155/2017/2580620. Epub 2017 Oct 25. PMID: 29209545; PMCID: PMC5676382.
27. Zhang CG, Li LL, Feng YY, Chen J. Stiff limb syndrome with lower limb myoclonus: a case report. Medicine (Baltimore). 2019;98(49):e18160. https://doi.org/10.1097/MD.0000000000018160. PMID: 31804328; PMCID: PMC6919430
28. Brown P, Rothwell JC, Marsden CD. The stiff leg syndrome. J Neurol Neurosurg Psychiatry. 1997;62(1):31–7. https://doi.org/10.1136/jnnp.62.1.31. PMID: 9010397; PMCID: PMC486692
29. Barker RA, Revesz T, Thom M, Marsden CD, Brown P. Review of 23 patients affected by the stiff man syndrome: clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry. 1998;65(5):633–40. https://doi.org/10.1136/jnnp.65.5.633. PMID: 9810930; PMCID: PMC2170335
30. Balint B, Bhatia KP. Stiff person syndrome and other immune-mediated movement disorders – new insights. Curr Opin Neurol. 2016;29(4):496–506. https://doi.org/10.1097/WCO.0000000000000351. PMID: 27262149
31. Galli JR, Austin SD, Greenlee JE, Clardy SL. Stiff person syndrome with Anti-GAD65 antibodies within the national veterans affairs health administration. Muscle Nerve. 2018;
32. Rossetto O, Pirazzini M, Fabris F, Montecucco C. Botulinum neurotoxins: mechanism of action. Handb Exp Pharmacol. 2021;263:35–47. https://doi.org/10.1007/164_2020_355. PMID: 32277300
33. Bach-Rojecky L, Relja M, Lacković Z. Botulinum toxin type A in experimental neuropathic pain. J Neural Transm (Vienna). 2005;112(2):215–9. https://doi.org/10.1007/s00702-004-0265-1. PMID: 15657640
34. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;1(358):137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 Jul 1. PMID: 28673722
35. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain.

2014;155(4):674–84. https://doi.org/10.1016/j.pain.2013.12.009. Epub 2013 Dec 11. PMID: 24333775; PMCID: PMC3960322
36. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107(1-2):125–33. https://doi.org/10.1016/j.pain.2003.10.008. PMID: 14715398
37. Mika J, Rojewska E, Makuch W, Korostynski M, Luvisetto S, Marinelli S, Pavone F, Przewlocka B. The effect of botulinum neurotoxin A on sciatic nerve injury-induced neuroimmunological changes in rat dorsal root ganglia and spinal cord. Neuroscience. 2011;23(175):358–66. https://doi.org/10.1016/j.neuroscience.2010.11.040. Epub 2010 Nov 25. PMID: 21111791
38. Bossowska A, Lepiarczyk E, Mazur U, Janikiewicz P, Markiewicz W. Botulinum toxin type A induces changes in the chemical coding of substance P-immunoreactive dorsal root ganglia sensory neurons supplying the porcine urinary bladder. Toxins (Basel). 2015;7(11):4797–816. https://doi.org/10.3390/toxins7114797. PMID: 26580655; PMCID: PMC4663534
39. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes -an evidence based review. Toxicon. 2018;147:120–8. https://doi.org/10.1016/j.toxicon.2018.01.017. Epub 2018 Feb 1. PMID: 29409817
40. Shin MC, Wakita M, Xie DJ, Yamaga T, Iwata S, Torii Y, Harakawa T, Ginnaga A, Kozaki S, Akaike N. Inhibition of membrane Na+ channels by A type botulinum toxin at femtomolar concentrations in central and peripheral neurons. J Pharmacol Sci. 2012;118(1):33–42. https://doi.org/10.1254/jphs.11060fp. Epub 2011 Dec 10. PMID: 22156364
41. Hong B, Yao L, Ni L, Wang L, Hu X. Antinociceptive effect of botulinum toxin A involves alterations in AMPA receptor expression and glutamate release in spinal dorsal horn neurons. Neuroscience. 2017;357:197–207. https://doi.org/10.1016/j.neuroscience.2017.06.004. Epub 2017 Jun 10. PMID: 28606856
42. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459. PMID: 31387301; PMCID: PMC6723487
43. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012;61(2):236–9. https://doi.org/10.1016/j.neuint.2012.05.001. Epub 2012 May 8. PMID: 22580329
44. Lacković Z. Botulinum toxin and pain. Handb Exp Pharmacol. 2021;263:251–64. https://doi.org/10.1007/164_2019_348. PMID: 32016565
45. Drinovac Vlah V, Filipović B, Bach-Rojecky L, Lacković Z. Role of central versus peripheral opioid system in antinociceptive and anti-inflammatory effect of botulinum toxin type A in trigeminal region. Eur J Pain. 2018;22(3):583–91. https://doi.org/10.1002/ejp.1146. Epub 2017 Nov 13. PMID: 29134730
46. Wang W, Kong M, Dou Y, Xue S, Liu Y, Zhang Y, Chen W, Li Y, Dai X, Meng J, Wang J. Selective expression of a SNARE-cleaving protease in peripheral sensory neurons attenuates pain-related gene transcription and neuropeptide release. Int J Mol Sci. 2021;22(16):8826. https://doi.org/10.3390/ijms22168826. PMID: 34445536; PMCID: PMC8396265
47. Hok P, Veverka T, Hluštík P, Nevrlý M, Kaňovský P. The central effects of botulinum toxin in dystonia and spasticity. Toxins (Basel). 2021;13(2):155. https://doi.org/10.3390/toxins13020155. PMID: 33671128; PMCID: PMC7922085
48. Choudhury S, Baker MR, Chatterjee S, Kumar H. Botulinum toxin: an update on pharmacology and newer products in development. Toxins (Basel). 2021;13(1):58. https://doi.org/10.3390/toxins13010058. PMID: 33466571; PMCID: PMC7828686
49. Manuel Muñoz-Lora VR, Abdalla HB, Del Bel Cury AA, Clemente-Napimoga JT. Modulatory effect of botulinum toxin type A on the microglial P2X7/CatS/FKN activated-pathway in antigen-induced arthritis of the temporomandibular joint of rats. Toxicon. 2020;187:116–21. https://doi.org/10.1016/j.toxicon.2020.08.027. Epub 2020 Sep 1. PMID: 32882256
50. Ma K, Zhu D, Zhang C, Lv L. Botulinum toxin type A possibly affects $Ca_v3.2$ calcium channel subunit in rats with spinal cord injury-induced muscle spasticity. Drug Des Devel Ther.

2020;14:3029–41. https://doi.org/10.2147/DDDT.S256814. PMID: 32801642; PMCID: PMC7395704
51. Vacca V, Madaro L, De Angelis F, Proietti D, Cobianchi S, Orsini T, Puri PL, Luvisetto S, Pavone F, Marinelli S. Revealing the therapeutic potential of botulinum neurotoxin type A in counteracting paralysis and neuropathic pain in spinally injured mice. Toxins (Basel). 2020;12(8):491. https://doi.org/10.3390/toxins12080491. PMID: 32751937; PMCID: PMC7472120
52. Waskitho A, Yamamoto Y, Raman S, Kano F, Yan H, Raju R, Afroz S, Morita T, Ikutame D, Okura K, Oshima M, Yamamoto A, Baba O, Matsuka Y. Peripherally administered botulinum toxin type A localizes bilaterally in trigeminal ganglia of animal model. Toxins (Basel). 2021;13(10):704. https://doi.org/10.3390/toxins13100704. PMID: 34678997; PMCID: PMC8541196
53. Marinelli S, Vacca V, Ricordy R, Uggenti C, Tata AM, Luvisetto S, Pavone F. The analgesic effect on neuropathic pain of retrogradely transported botulinum neurotoxin A involves Schwann cells and astrocytes. PLoS One. 2012;7(10):e47977. https://doi.org/10.1371/journal.pone.0047977. Epub 2012 Oct 24. PMID: 23110146; PMCID: PMC3480491
54. Bach-Rojecky L, Lacković Z. Central origin of the antinociceptive action of botulinum toxin type A. Pharmacol Biochem Behav. 2009;94(2):234–8. https://doi.org/10.1016/j.pbb.2009.08.012. Epub 2009 Sep 2. PMID: 19732788
55. Spillane JD, Nathan PW, Kelly RE, Marsden CD. Painful legs and moving toes. Brain. 1971;94(3):541–56. https://doi.org/10.1093/brain/94.3.541. PMID: 4255783
56. Ebersbach G, Schelosky L, Schenkel A, Scholz U, Poewe W. Unilateral painful legs and moving toes syndrome with moving fingers--evidence for distinct oscillators. Mov Disord. 1998;13(6):965–8. https://doi.org/10.1002/mds.870130617. PMID: 9827623
57. Eisa M, Singer C, Sengun C, Russel A, Jabbari B, Papapetropoulos S. Treatment of painful limbs/moving extremities with botulinum toxin type A injections. Eur Neurol. 2008;60(2):104–6. https://doi.org/10.1159/000138962. Epub 2008 Jun 14. PMID: 18552499
58. Alvarez MV, Driver-Dunckley EE, Caviness JN, Adler CH, Evidente VG. Case series of painful legs and moving toes: clinical and electrophysiologic observations. Mov Disord. 2008;23(14):2062–6. https://doi.org/10.1002/mds.22272. PMID: 18759340
59. Nathan PW. Painful legs and moving toes: evidence on the site of the lesion. J Neurol Neurosurg Psychiatry. 1978;41(10):934–9. https://doi.org/10.1136/jnnp.41.10.934. PMID: 215727; PMCID: PMC493198
60. Schott GD. "Painful legs and moving toes": the role of trauma. J Neurol Neurosurg Psychiatry. 1981;44(4):344–6. https://doi.org/10.1136/jnnp.44.4.344. PMID: 6113273; PMCID: PMC490959
61. Miyakawa T, Yoshimoto M, Takebayashi T, Yamashita T. Case reports: painful limbs/moving extremities: report of two cases. Clin Orthop Relat Res. 2010;468(12):3419–25. https://doi.org/10.1007/s11999-010-1437-y. Epub 2010 Jun 29. PMID: 20585912; PMCID: PMC2974875
62. Okuda Y, Suzuki K, Kitajima T, Masuda R, Asai T. Lumbar epidural block for 'painful legs and moving toes' syndrome: a report of three cases. Pain. 1998;78(2):145–7. https://doi.org/10.1016/S0304-3959(98)00129-8. PMID: 9839826
63. Takahashi H, Saitoh C, Iwata O, Nanbu T, Takada S, Morita S. Epidural spinal cord stimulation for the treatment of painful legs and moving toes syndrome. Pain. 2002;96(3):343–5. https://doi.org/10.1016/S0304-3959(01)00479-1. PMID: 11973008
64. Dressler D, Thompson PD, Gledhill RF, Marsden CD. The syndrome of painful legs and moving toes. Mov Disord. 1994;9(1):13–21. https://doi.org/10.1002/mds.870090104. PMID: 7511213
65. Jabbari B, Molloy FM, Erickson M, Floeter MK. Bilateral painful hand-moving fingers: electrophysiological assessment of the central nervous system oscillator. Mov Disord. 2000;15(6):1259–63. https://doi.org/10.1002/1531-8257(200011)15:6<1259::aid-mds1032>3.0.co;2-5. PMID: 11104217
66. Nishioka K, Suzuki M, Nakajima M, Hara T, Iseki M, Hattori N. Painful legs and moving toes syndrome evaluated through brain single photon emission computed tomography: a case

series. J Neurol. 2019;266(3):717–25. https://doi.org/10.1007/s00415-019-09194-3. Epub 2019 Jan 14. PMID: 30637456
67. Kawajiri S, Noda K, Ikeda A, Koinuma T, Tomizawa Y, Hattori N, Okuma Y. Low dose of clonazepam is effective in the treatment of painless legs and moving toes syndrome: a case report. Case Rep Neurol. 2015;7(1):59–62. https://doi.org/10.1159/000380942. PMID: 25873890; PMCID: PMC4395820
68. Beckmann Y, Gürgör N, Bülbül NG, Seçil Y, Türkmen N. Painful legs and moving toes syndrome: responsive to dopaminergic treatment. Acta Neurol Belg. 2015;115(1):87–8. https://doi.org/10.1007/s13760-014-0303-1. Epub 2014 May 10. PMID: 24817382
69. Reich SG. Painful legs and moving toes. Handb Clin Neurol. 2011;100:375–83. https://doi.org/10.1016/B978-0-444-52014-2.00029-X. PMID: 21496596
70. Schoffer K. Painful leg moving toes treated with botulinum toxin type A: a video report. Mov Disord. 2010;25(6):784–5. https://doi.org/10.1002/mds.22869. PMID: 20310048
71. Rodriguez RL, Fernandez HH. Sustained benefit of painful legs moving toes syndrome with botulinum toxin type A. J Clin Neurosci. 2013;20(7):1031–2. https://doi.org/10.1016/j.jocn.2012.06.016. Epub 2013 Apr 9. PMID: 23582954
72. Bosco L, Falzone YM, Butera C, Bianchi F, Vezzulli P, Filippi M, Del Carro U. Painful legs and moving toes syndrome: treating movement to treat pain-a case report. J Neurol. 2020;267(6):1852–4. https://doi.org/10.1007/s00415-020-09878-1. Epub 2020 May 5. PMID: 32372183
73. Rosanoff S. La camptocormie. Rev Neurol. 1915;22:937–9.
74. Brodie BC. Pathological and surgical observations on the diseases of the joints. London: Longman; 1818. p. 276.
75. Finsterer J, Strobl W. Presentation, etiology, diagnosis, and management of camptocormia. Eur Neurol. 2010;64(1):1–8. https://doi.org/10.1159/000314897. Epub 2010 Jun 8. PMID: 20634620
76. Ali F, Matsumoto JY, Hassan A. Camptocormia: Etiology, diagnosis, and treatment response. Neurol Clin Pract. 2018;8(3):240–8. https://doi.org/10.1212/CPJ.0000000000000453. PMID: 30105164; PMCID: PMC6075991
77. Azher SN, Jankovic J. Camptocormia: pathogenesis, classification, and response to therapy. Neurology. 2005;65:355–9.
78. Melamed E, Djaldetti R. Camptocormia in Parkinson's disease. J Neurol. 2006;253(Suppl 7):VII 14–6.
79. Djaldetti R, Mosberg-Galili R, Sroka H, Merims D, Melamed E. Camptocormia (bent spine) in patients with Parkinson's disease--characterization and possible pathogenesis of an unusual phenomenon. Mov Disord. 1999;14(3):443–7. https://doi.org/10.1002/1531-8257(199905)14:3<443::aid-mds1009>3.0.co;2-g. PMID: 10348467
80. Bloch F, Houeto JL, Tezenas du Montcel S, Bonneville F, Etchepare F, Welter ML, T, Behar C, Lazennec JY, Kurys E, Arnulf I, Bonnet AM, Agid Y. Parkinson's disease with camptocormia. J Neurol Neurosurg Psychiatry. 2006;77:1223–8.
81. Zhang LY, Cao B, Wei QQ, Ou RW, Zhao B, Yang J, Wu Y, Shang HF. Camptocormia in patients with multiple system atrophy at different disease durations: frequency and related factors. BMC Neurol. 2021;21(1):181. https://doi.org/10.1186/s12883-021-02210-y. PMID: 33910524; PMCID: PMC8080355
82. Kaji S, Shibayama H, Sato S, Fukutake T. Acute camptocormia as the presenting symptom of tetanus. J Neurol Neurosurg Psychiatry. 2014;85(8):936–7.
83. Reese R, Knudsen K, Falk D, Mehdorn HM, Deuschl G, Volkmann J. Motor outcome of dystonic camptocormia treated with pallidal neurostimulation. Parkinsonism Relat Disord. 2014;20(2):176–9. https://doi.org/10.1016/j.parkreldis.2013.10.022. Epub 2013 Nov 1. PMID: 24268100
84. Lyons M, Boucher O, Patel N, Birch B, Evidente V. Long-term benefit of bilateral subthalamic deep brain stimulation on camptocormia in Parkinson's disease. Turk Neurosurg. 2012;22(4):489–92. https://doi.org/10.5137/1019-5149.JTN.3857-10.0. PMID: 22843472

85. Margraf NG, Wrede A, Rohr A, Schulz-Schaeffer WJ, Raethjen J, Eymess A, Volkmann J, Mehdorn MH, Jansen O, Deuschl G. Camptocormia in idiopathic Parkinson's disease: a focal myopathy of the paravertebral muscles. Mov Disord. 2010;25(5):542–51. https://doi.org/10.1002/mds.22780. PMID: 20108372
86. Sancho Saldaña A, Lázaro Romero A, Capablo Liesa JL, Alarcia AR. Camptocormia as the main manifestation of a mutation in the POLG gene. Neurologia (Engl Ed). 2021;36(5):390–2. https://doi.org/10.1016/j.nrleng.2020.07.015. Epub 2021 Mar 23. PMID: 34714238
87. Ma H, McEvoy KM, Milone M. Sporadic inclusion body myositis presenting with severe camptocormia. J Clin Neurosci. 2013;20(11):1628–9. https://doi.org/10.1016/j.jocn.2013.06.004. Epub 2013 Sep 19. PMID: 24055211
88. Oravivattanakul S, Abboud H, Fernandez H, Itin I. Unusual case of levodopa-responsive camptocormia in a patient with negative dopamine transporter scan and normal DYT 5 gene. Clin Neuropharmacol. 2014;37(2):63–4. https://doi.org/10.1097/WNF.0000000000000024. PMID: 24614670
89. Arii Y, Sawada Y, Kawamura K, Miyake S, Taichi Y, Izumi Y, Kuroda Y, Inui T, Kaji R, Mitsui T. Immediate effect of spinal magnetic stimulation on camptocormia in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2014;85(11):1221–6. https://doi.org/10.1136/jnnp-2014-307651. Epub 2014 Apr 29. PMID: 24780955
90. Lai Y, Song Y, Su D, Wang L, Zhang C, Sun B, Nonnekes J, Bloem BR, Li D. Pallidal stimulation as treatment for camptocormia in Parkinson's disease. NPJ Parkinsons Dis. 2021;7(1):8. https://doi.org/10.1038/s41531-020-00151-w. Erratum in: NPJ Parkinsons Dis. 2021 Mar 29;7(1):32. PMID: 33462205; PMCID: PMC7813849
91. Kataoka H, Tonomura Y, Eura N, Terashima M, Kawahara M, Ueno S. Painful abdominal contractions in patients with Parkinson disease. J Clin Neurosci. 2012;19(4):624–7. https://doi.org/10.1016/j.jocn.2011.06.026. Epub 2012 Jan 30. PMID: 22285116
92. Dupeyron A, Stober N, Gelis A, Castelnovo G, Labauge P, Pélissier J. Painful camptocormia: the relevance of shaking your patient's hand. Eur Spine J. 2010;July19 Suppl 2:S87–90.
93. Wijemanne S, Jimenez-Shahed J. Improvement in dystonic camptocormia following botulinum toxin injection to the external oblique muscle. Parkinsonism Relat Disord. 2014;20(10):1106–7. https://doi.org/10.1016/j.parkreldis.2014.06.002. Epub 2014 Jun 16. PMID: 24981917
94. von Coelln R, Raible A, Gasser T, Asmus F. Ultrasound-guided injection of the iliopsoas muscle with botulinum toxin in camptocormia. Mov Disord. 2008;23(6):889–92. https://doi.org/10.1002/mds.21967. PMID: 18307265
95. Colosimo C, Salvatori FM. Injection of the iliopsoas muscle with botulinum toxin in camptocormia. Mov Disord. 2009;24(2):316–7. https://doi.org/10.1002/mds.22249. PMID: 18973251
96. Jankovic J. An update on new and unique uses of botulinum toxin in movement disorders. Toxicon. 2018;147:84–8. https://doi.org/10.1016/j.toxicon.2017.09.003. Epub 2017 Sep 6. PMID: 28888928
97. Jindal P, Jankovic J. Botulinum toxin in Parkinson's disease and atpical Parkinson disorders. In: Jabbari B, editor. Botulinum toxin treatment in clinical medicine. A disease oriented approach. Camptocormia – page 35. Cham: Springer; 2018.
98. Jabbari B, Maher N, Difazio MP. Botulinum toxin a improved burning pain and allodynia in two patients with spinal cord pathology. Pain Med. 2003;4(2):206–10. https://doi.org/10.1046/j.1526-4637.2003.03013.x. PMID: 12873271
99. Park J, Chung ME. Botulinum toxin for central neuropathic pain. Toxins (Basel). 2018;10(6):224. https://doi.org/10.3390/toxins10060224. PMID: 29857568; PMCID: PMC6024683

Chapter 18
Botulinum Toxins for Treatment of Cancer-Related and End of Life Pain

Introduction

Patients affected by cancer often experience pain through different mechanisms. A cancerous tissue, primary or metastatic, can cause pain due to direct pressure over the adjacent structures. Pain can occur at the site of cancer resection (post-surgical) or as local pain at the site of radiation. Chemotherapy for cancer often damages peripheral nerves and causes painful peripheral neuropathy.

In a comprehensive review of this subject, Glare et al. [1] found that post-surgical pain is a common complaint in several cancers. The incidence of pain is cited as 25–60% after thoracotomy, 50% after mastectomy, 39% after axillary node dissection, 13–25% as phantom breast pain, 38% in female cervical cancer, and 42% after radical neck dissection [2–9]. In one review 55% of the patients with metastatic cancer suffered from chronic pain [10]. Others have reported that approximately 25% of patients who undergo radiation or surgery for cancer develop pain at/or close to the area of local radiation or surgery [11, 12]. List and Bilir [13] observed post-radiation pain in 15–30% of their patients with head and neck cancer which they attributed to the development of fibrosis, scar, and keloid tissue.

In general, 5–10% of cancer survivors suffer from chronic severe pain that impairs their quality of life and interferes with their daily functions [1]. Advanced cancer is associated with severe pain in 70–80% of patients [14]. The prevalence of severe pain in advanced cancer, however, is similar to that of other chronic and advanced medical disorders [15]. For instance, the estimated prevalence of pain in chronic heart disease and chronic obstructive pulmonary disease has been reported as 44–77% and 34–77%, respectively [16, 17].

Palliative treatment of cancer-related pain is often difficult since side effects of analgesic medications are poorly tolerated by debilitated patients. For local pain after surgery and radiotherapy or painful neuropathy resulting from chemotherapy, topical application of trolamine, calendula officinalis, hyaluronic acid, and

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_18

lidocaine patch may provide transient relief [18–20]. However, sustained relief is uncommon and was noted in only 25% of patients who applied lidocaine patch to the allodynic region [21]. For painful neuropathy induced by chemotherapy, the first line of treatment drugs consists of tricyclic antidepressants, pregabalin, gabapentin, and selective serotonin norepinephrine reuptake inhibitors followed by lidocaine patches and capsaicin, high-concentration, patches. Treatment with cannabinoid ointments is currently being studied, but the early results are inconclusive [22].

For severe and sustained pain, opioid analgesics are recognized as the leading source of pharmacotherapy [23]. Although effective in relieving cancer-related pain, chronic opioid use is complicated by undesirable side effects such as nausea, somnolence, and constipation, each noted in more than 20% of the patients [24]. Furthermore, chronic use promotes opioid abuse and addiction. The opioid crisis that began around 1990 reached pandemic proportions in 2017, claiming 91 lives per day in the United States (Department Human and Health Services statement).

Considering the serious issues inherent in opioid use, in recent years, pain specialists have focused on investigation of the analgesic effects of cannabinoids in cancer pain. Animal studies in well-designed models of pain support the analgesic effect of cannabinoids [25, 26]. In human, however, data from cannabinoid use in cancer pain is not yet convincing. A recent review and meta-analysis of 36 clinical trials with cannabinoids in different human pain disorders (including cancer pain) has judged all studies to be as low or very low quality and tinted by high degrees of bias [27]. The recent (2021) report of the International Society of Pain Presidential Task Force outlines the gaps of knowledge in this area of medical therapeutic and defines key areas where high-quality clinical trials with cannabinoids are needed in pain medicine [28]. In a recently reported (2021) Danish survey [29], the report showed that 13% of the cancer patients used cannabis. Among users, 83% reported a satisfactory response. Cannabis was used mainly for pain relief, improvement of nausea after chemotherapy, and for regulating sleep. In a recently reported US survey (2021), however, the percent of cancer patients with cannabis use was lower (8%), even lower than the general population [30].

Botulinum Neurotoxin Therapy for Post-surgical/ Post-radiation Pain in Cancer Patients

In animal models of pain, botulinum neurotoxins (BoNTs) have shown efficacy in relieving pain via different mechanisms. Both types A and B toxin can reduce effect of pain transmitters such as glutamate, calcitonin gene-related peptide, and substance P after intramuscular or subcutaneous/intradermal injection. These analgesic effects of the BoNTs are exerted upon the peripheral nerve terminals as well as the central sensory neurons. Moreover, BoNT-A blocks the function of sodium channels that are essential for transmission of the nociceptive signals to the central nervous system. BoNTs suppress the discharge of intrafusal muscle fibers after intramuscular injection, an action that by reducing the intrafusal input to the spinal

cord can reduce central sensitization [31–50]. In chronic pain, the peripheral sensitization of nerve terminals or peripheral neurons gradually increases the sensitivity of central neurons leading to central sensitization that further increases the intensity of perceived pain [51].

The literature on the effect of botulinum toxin injection upon cancer pain is limited to two double-blind, placebo-controlled studies and a few open-label prospective and retrospective observations (Table 18.1). In addition, several case reports have described the positive effect of botulinum toxin therapy upon pain related to cancer and chemotherapy and post-surgical pain. Several case reports representing my own experience with botulinum toxin therapy for cancer-related pain are also presented in this chapter.

Double-Blind, Placebo-Controlled Studies (Table 18.1: [59–61])

In 2018 and 2020, De Groef et al. published the results of two double-blind, placebo-controlled studies [59, 60] investigating the effect of onaA (Botox) injections into pectoralis muscle of patients with breast cancer. Patients had local chest pain either after radiation and surgery or after chemotherapy. Fifty patients were included in each study. In the toxin group, each patient received a single injection of 100 units into the pectoralis major. The placebo group perceived the same volume of saline into the same muscle. The patient's pain response to BoNT therapy was assessed by VAS (0–10 scale) at three months post-injection. There was no significant improvement of pain or function in either study group after BoNT-A injections.

Niak et al. [61] conducted a blinded and controlled study on 18 patients with painful leiomyomas. The authors injected 5 units of botulinum toxin A (Botox) into the painful lesions and compared the toxin effect with saline injections. Patients' pain was evaluated by VAS and brief pain inventory, and the change in quality of life was assessed by Dermatology Life Quality Index (DLQI). The primary outcome measure was the difference in average regional pain before and after ice provocation over a 4-week period. The authors found significant improvement in patients' quality of life ($P = 0.007$) among patients who had received BoNT injections. Those patients who had received BoNT-A injection also demonstrated improvement of their pain compared to those who had received saline injections, but the difference did not reach statistical significance ($P = 0.06$).

Retrospective Studies

In a study by Van Daele et al. [52], injection of onabotulinumtoxinA into the tight and painful sternocleidomastoid muscle relieved the pain and tightness in four of six patients. All patients had received radiotherapy for head and neck cancer. The

Table 18.1 Blinded and open-label studies investigating the efficacy of BoNT injections in cancer-related pain

Author and date	Study type	Number patients	Toxin type	Toxin units	Cancer location	Treatment	Primary outcome	Results
Van Daele et al., 2002 [52]	R	6	BoNT-A	20–25	Head, neck	Radiation Chemotherapy	Pain	Complete pain relief in four of six patients
Wittkindt et al., 2006 [53]	P	23	BoNT-A	60–120; 160–240	Head, neck	Radiation, surgery	Pain (VAS) at day 28 post-surgery	Low dose improved pain ($P < 0.05$)
Hartel et al., 2008 [54]	P	19	onaA and aboA	50 and 250	Head, neck	Chemotherapy radiation	Pain (VAS); Function	VAS ($P = 0.02$) Function ($P = 0.04$)
Stubblefield et al., 2008 [55]	R	23	onaA	50–200	Head, neck	Radiation, surgery	Pain	Improved 87%
Mittal et al., 2014 [56]	R	7	onaA	100	Head, neck, breast	Radiation, surgery	Pain (VAS); PGIC at wk 4 post-surgery	VAS improved ($P < 0.05$). five of seven patients reported improvement od quality of life
Bach et al., 2012 [57]	P	9	aboA	100–140 (SCM); 125–200 (PF)	Head, neck	Radiation, surgery	Pain (VAS) and FDSNP at wk 4 post-surgery	Both pain and FDSNP improved ($P = 0.01$)
Rostami et al., 2014 [58]	P	12	incoA	100	Head, neck, breast	Radiation, surgery	Pain (VAS) and PGIC, at wk 6	Both pain and PGIC improved ($P < 0.05$)
De Groef et al., 2018 [59]	DPC	50	onaA	100 Pectoralis	Breast	Radiation surgery	Pain (VAS), at 12 wks post-injection	No significant difference in pain intensity between toxin and placebo groups
De Groef et al., 2020 [60]	DPC	50	onaA	100 in a single injection into pectoralis	Breast	Chemotherapy	Pain (VAS), at 12 wks Function	No improvement of pain and function

Naik et al., 2015 [61]	DPC	18	BoNT-A	5 units/lesion	Cutaneous painful leiomyomas	Painful Leiomyomas	Pain (VAS);DLQI	Trend of improvement in VAS ($P = 0.06$) DLQI improved: ($P = 0.007$)
Vuong et al., 2012 [62]	P	15	onaA	100	Rectal cancer , radiation proctitis	High dose endorectal brachytherapy (HDBERT)	Pain (VAS)	Lower incidence of radiation prostatitis and bowel urgency ($p < 0.05$), Reduced pain ($P = 0.007$)

P prospective, *R* retrospective, *DPC* double-blind, placebo-controlled, *VAS* visual analog scale, *PGIP* Patient Global Impression of Pain, *FDSNP* functional disability scale for neck pain, *SCM* sternocleidomastoid, *PF* pectoralis flap, *DLQI* Dermatology Life Quality Index. OnaA (Botox), IncoA(Xeomin), aboA (Dysport)

injected dose was 20–25 units administered at one or two points into the sternocleidomastoid muscle.

Stubblefield et al. [55] also found BoNT-A injection helpful in relieving focal pain caused by radiation fibrosis. In this retrospective study of 23 patients, 30% had painful trismus, and 43% had trigeminal and cervical plexus neuralgia.

Voung et al. [62] studied the effect of BoNT injection into the rectal wall immediately after high dose-rate-endorectal brachytherapy (HDREBT) in 15 patients with prostatic cancer. The patients who received 100 units of onaA into the rectal wall had a lower incidence of acute radiation prostatitis with significant reduction of bowel frequency and urgency ($P < 0.05$) and lesser degrees of pain ($P = 0.07$).

In another study [57] of nine patients with post-surgical contracture of sternocleidomastoid or pectoralis major muscle related to head and neck cancer, patients expressed pain relief after administration of aboA into sternocleidomastoid muscle (100–400 units) or the pectoralis muscle flap (125–200 units) with no side effects. Injections were administered at four to five locations into the sternocleidomastoid muscle or into the pectoralis muscle flap.

Mittal et al. [56] studied the results of onaA (Botox) injections into the neck and jaw muscles in seven patients with head and neck cancers. Patients had local pain after surgery or radiation. The dose of injected toxin varied from 20 to 100 units depending on the location of pain and the extent of the painful area. All seven patients experienced significant improvement in pain (an average drop of 5.1 points in VAS). In six of seven patients, pain relief was associated with improvement of quality of life. Five patients rated their improvement as very satisfactory in the Patient's Global Impression of Change (PGIC).

Prospective Studies

Wittekindt et al. [53] examined the efficacy of BoNT-A (type not specified) in 23 patients who reported neuropathic pain in the neck and shoulder following neck dissection surgery for squamous cell carcinoma of upper "aero-digestive tract." BoNT-A was diluted with 1 or 2 cc of preservative-free saline before administration. Patients were divided into low dose (80–120 units) and high dose (160–240 units) groups. Patients and physicians were blinded to the dose of injections. Injections were performed in two to eight locations subcutaneously into targeted neck and shoulder regions. Patients' response to BoNT injection was measured by visual analog scale (VAS) at baseline prior to injections and at day 28 after injections. The mean baseline pain was 4.3 on VAS (0–10) scale. The quality of life was evaluated by a questionnaire from the European Organization for Research and Treatment of Cancer (EORTC), specifically prepared for head and neck cancers, at the same time frames. On day 28, mean VAS score for the low dose group changed from 4.3 to 3.6 ($P < 0.05$); the high dose group improved also, but the change was not statistically significant. Furthermore, the low dose group also showed a trend for improvement in quality of life that was not observed in the high dose group.

In another prospective study [54], the efficacy of onabotulinumtoxinA (OnaA) and abobotulinum toxinA (AboA) was assessed in 19 patients with nasopharyngeal and oropharyngeal cancer who developed severe spasm of masseter muscles and trismus, on the average, 5.6 years after radiotherapy for cancer. Eleven patients had received chemotherapy in addition to radiation. The location of cancers was in the nasopharynx ($n = 3$), oropharynx ($n = 9$), oral cavity ($n = 2$), oral cavity and nasopharynx ($n = 1$), larynx ($n = 3$), and parotid gland ($n = 1$). Each masseter muscle was injected at two points, either with onaA (50 units) or aboA (250 units). At 4 weeks post-injection, pain, spasms, and functional score (measured in a 20-subset questionnaire) all improved significantly compared to baseline ($P = 0.002$, $P = 0.004$, and $P = 0.04$, respectively). No difference was noted between onaA and AboA.

Rostami et al. [58] prospectively studied the effect of incobotulinumtoxinA (inco-A- Xeomin) on 12 patients who had developed moderate to severe focal pain (VAS > 5) at the site of cancer resection or cancer radiation. Patients had breast or head and neck cancer. All patients had failed at least two analgesic medications. Efficacy of treatment was measured by VAS, Patient's Global Impression of Change (PGIC), and Quality of Life Scale for pain at 4, 6, 8, 10, and 12 weeks post-injection. The primary outcome was two grades or more improvement in VAS and patient's level of satisfaction expressed in PGIC at 4 weeks. The secondary outcome was improvement of quality of life at 6 weeks. Patients were injected with up to 100 units of incobotulinumtoxin A (IncoA) intramuscularly or subcutaneously depending on the type and location of their pain. Two patients passed away during the course of the study, one dropped out due to a skin reaction, and another patient could not return for the follow-up due to his poor general condition. All of the eight remaining subjects (age 31–70, four female) demonstrated significant improvement of their pain assessed by visual analog scale (VAS) (3–9 degrees reduction, average 3.9 degrees). In Patient's Global Impression of Change scale (PGIC), seven out of eight patients reported their pain as "much improved." Three of the eight patients reported significant improvement of their quality of life. None of the patients reported any serious side effect.

In addition to abovementioned case series and double-blind, placebo-controlled studies, several case reports have described a positive effect with botulinum toxin injections in relief of pain in patients with cancer. Two of these reports are presented below:

1. *Rectal Pain and Radiation-Induced Proctitis* [63]: A 75-year-old man with history of rectal cancer and severe radiation-induced proctitis developed severe rectal pain and a large noncancerous rectal ulcer after local resection and radiation. Injection of 100 units of onaA into the rectal wall, all around the sphincter, reduced the pain dramatically. After 48 hours, the analgesic drug delivery system could be removed. Months later, endoscopic examination disclosed reduction in size of the recto-sigmoidal ulcer. The preexisting rectal incontinence worsened after onaA injection but recovered in 4 days.
2. *Painful Raynaud Syndrome Due to Chemotherapy* [64]: A 56-year-old female with non-small cell lung cancer (NSCLC) developed Raynaud's syndrome fol-

lowing chemotherapy with bevacizumab and pemetrexed. She had progressive discoloration and pain at her fingertips that progressed to ischemia and dry gangrene. Medical management was not helpful, and the patient was in danger of losing her fingers. To relieve severe pain, she was injected with a total of 90 units of onaA intradermally in nine sites (10 units per site) into palm of the hand and wrist (Fig. 18.1). Over the next 5–7 days, the patient reported significant improvement of her pain associated with visible improvement of temperature and color of the digits. Over the next 18 months before she succumbed to the disease, she reported high satisfaction with onaA injections.

The following cases are presented from the author's experience with BoNT therapy for post-radiation/post-surgical pain in cancer patients.

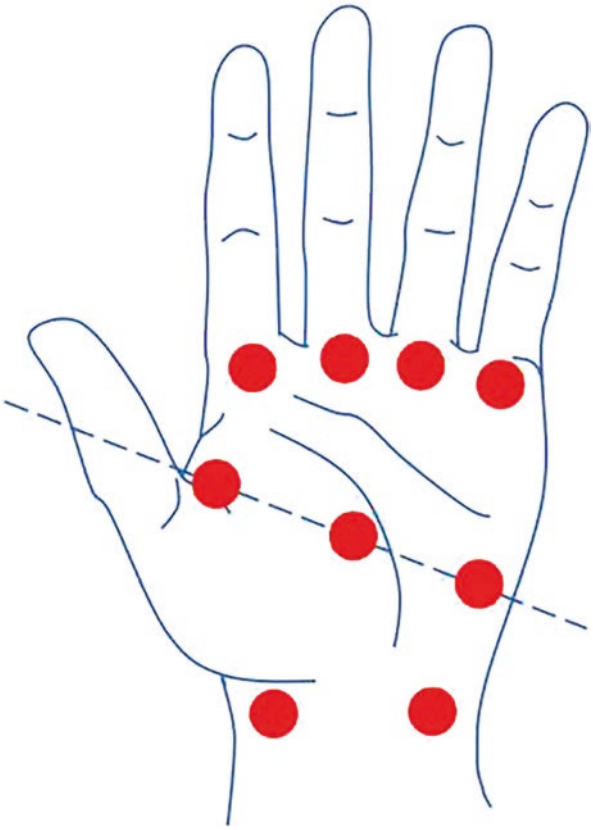

Fig. 18.1 The site of BoNT-A injections in the patient with chemotherapy-induced Raynaud syndrome [64]. (Reproduced under creative commons attribution license. Courtesy of Cureus publishing)

Case 1: Carcinoma of the Base of the Tongue Associated with Painful Upper Neck Spasms and Burning Pain Interfering with Speaking and Swallowing

A 47-year-old, right-handed male was referred to the Yale Neurotoxin Treatment Clinic for evaluation of right upper neck pain and difficulty in swallowing and speaking of 5 years duration. Six years ago, he was found to have a tumor at the base of his tongue with cervical lymphadenopathy on the right side. He underwent resection of the tumor with removal of lymph nodes and neck muscles on the right side. The tumor was a squamous cell carcinoma. Shortly after resection, he received radiotherapy to the base of the tongue and right side of the neck. A few months later, he experienced tingling and pulling of the base of the tongue which gradually evolved into painful spasms and burning sensation below the angle of the right jaw interfering with speaking and eating. Treatment with a variety of analgesic drugs was only minimally helpful. The patient's general medical and neurological examinations were normal except for loss of muscles on the right side of the neck and mild weakness of the tongue. A vertical surgical scar was visible on the right side of the neck extending from the lower neck to the lower edge of the mandible. Several areas of induration and keloid formation were present, the hardest and most painful being located anterior and slightly below the angle of the right jaw (Fig. 18.2).

Twenty units of onabotulinumtoxinA were injected into each of the three areas of indurated scar tissue on the right side of the neck (Fig. 18.2). The dilution was 100 units/cc of normal saline. A ¾ inch long, 27.5 gauge needle was used for injections. After a week, the patient reported total cessation of muscle spasms and burning pain as well as marked improvement of his swallowing and speech. He reported no side effects. The pain and discomfort returned after six months. Over the next 7 years, the patient continued to receive onaA injections into the same cervical regions, with a slightly higher dose of onaA (30, 30, and 20 units) over the last four years. The injections, employed at six-month intervals, remained efficacious over 7 years of follow-up.

Case 2: Intense Left Cervical Pain Following Laryngectomy and Neck Dissections for Squamous Cell Carcinoma of the Piriform Sinus

A 48-year-old male underwent laser supraglottic laryngectomy with bilateral neck dissections for squamous cell carcinoma of the left piriform sinus. This was followed by courses of chemotherapy and radiation. Two years later, the patient developed intense left cervical pain and left shoulder pain beginning with spasms of the left sternocleidomastoid (SCM) muscle. The pain was described as deep and aching but at times sharp and jabbing. A variety of medications including fentanyl (25 mcg/h) patch and hydromorphone (2 mg tablets), given as needed, provided no significant pain relief. He was then injected with a total dose of 200 units of

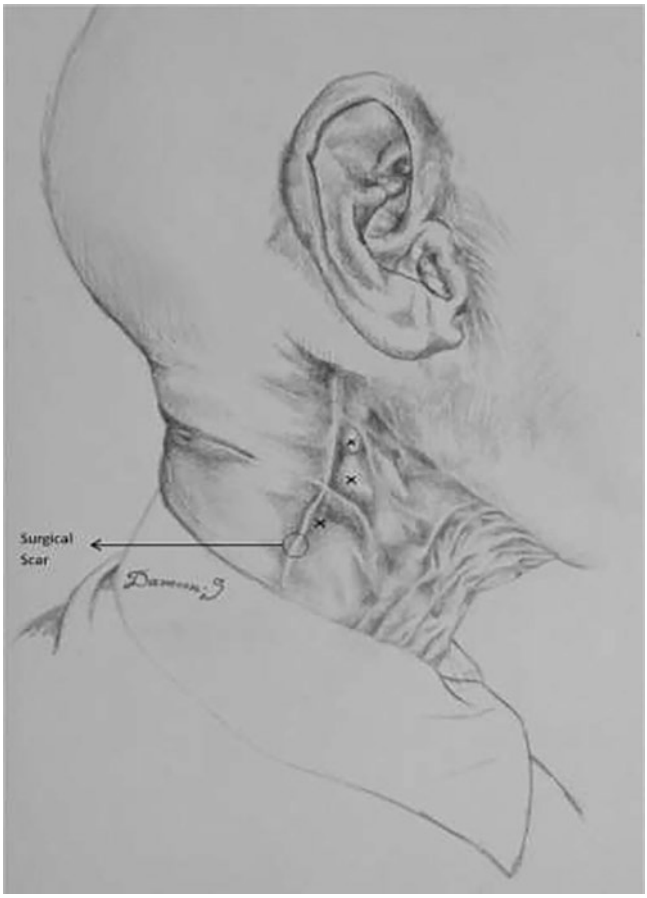

Fig. 18.2 (Case 1): Focal pain and spasms on the right side of the neck after resection of carcinoma of the base of the tongue. Sites of injections (x) into indurated muscle and scar tissue. (Drawing courtesy of Damoun Safarour, M.D.)

onabotulinumtoxinA into the left sternocleidomastoid, left trapezius, left splenius, and left levator scapulae muscles at several points, 15–20 units per site (Fig. 18.3). After a week, he reported marked reduction of pain (VAS score dropped from 8 to 1); on PGIC, he expressed the outcome as "very satisfactory." The response continued over a period of 3 years with repeat injections performed every 4 months. The patient did not report any side effects.

Case 3: Severe Spasms of Masseter Muscles 6 Months After Resection and Radiation of a Left Tonsillar Cancer

A 54-year-old male with a history of left-sided tonsillar cancer had undergone surgical resection and radiation therapy. Six months later, he noted painful spasm of the right masseter and pain during eating or jaw opening. This eventually spread to the

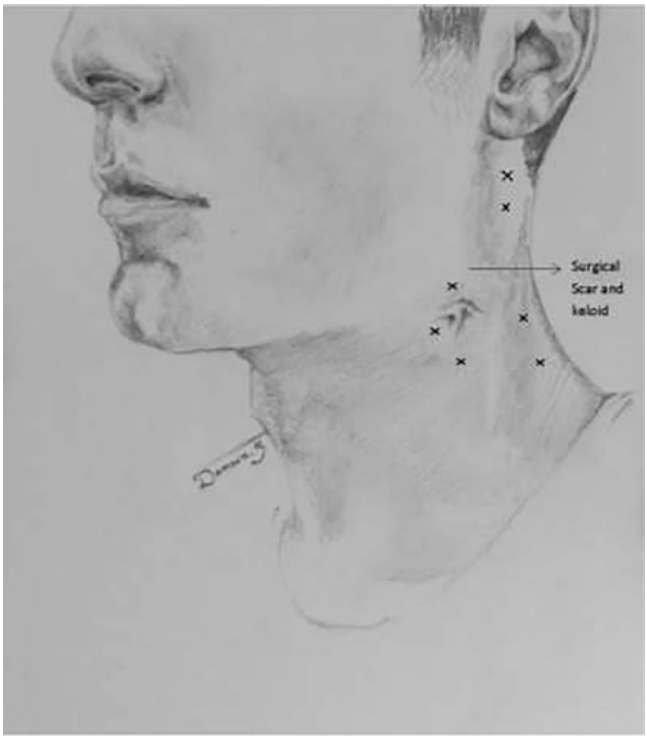

Fig. 18.3 (Case 2): Intense left cervical pain after radical neck dissection (squamous cell carcinoma of the pyriform sinus). Sites of BoNT injections (x). (Drawing courtesy of Damoun Safarpour, M.D.)

left masseter and to the upper neck regions. The pain became excruciating during jaw opening, eating, and chewing. Baclofen, 20 mg daily, combined with a variety of analgesics offered little help. At Yale Botulinum Neurotoxin Clinic, he was injected with onaA into the masseter muscles bilaterally.

Each masseter received 60 units of onaA, injected into two sites (30unit per site). The total dose for both masseters was 120 units. The patient reported significant reduction of his pain after 10 days. The pain intensity score of 9 in VAS recorded at baseline changed to 1 at 4 weeks. He reported no side effects and, using the PGIC scale, reported pain relief after treatment as "very satisfactory." The pain returned, though less intense, after three months. Repeat injections every three months thereafter had the same beneficial effect. Over a six-year follow-up, he continued responding to BoNT injections every 3–4 months. For the last two years of his follow-up, the dose of the toxin was reduced to 50 units per masseter.

Comments

Botulinum neurotoxins influence the pain system through both peripheral and central mechanisms. Animal studies have shown that the analgesic effect of the toxin results, for the most part, from reducing production or action of several known pain

transmitters such a calcitonin gene-related peptide (CGRP), substance P, and glutamate [32–50]. These analgesic effects of BoNTs have been shown also in several human clinical pain syndromes such as chronic migraine, trigeminal, post-herpetic, and post-traumatic trigeminal neuralgias as well as pain of diabetic neuropathy [65–74].

In head and neck cancer, the results of BoNT injections on a total of 79 patients (from multiple studies) were uniformly positive, albeit no blinded studies are yet available (Table 18.1). This agrees with the author' s experience with BoNT therapy in 20 patients with head and neck cancer. In these patients, injections are done either into the neck muscles or around neck scars or into masseter muscles. In my view, the analgesic effect of the toxin for this indication is both due to relaxation of indurated muscles (especially in the neck) as well as the effect of the toxin upon peripheral nerve terminals and its inhibitory act on pain transmitters.

The effect of BoNTs on pain after mastectomy and/or post-mastectomy radiation remains controversial. Few patients in open trials [56, 58] described pain relief after BoNT injections. Two double-blind, placebo-controlled studies, however, found no statistically significant difference between toxin and placebo injections [59, 60]. For this indication (as in other indications of BoNT therapy), technical issues may influence the results. In these two negative studies [59, 60], the patients received a single injection of the toxin into the pectoralis muscle. However, in post-mastectomy expander reconstruction studies, significant pain relief resulted from multiple site injection of BoNTs into the pectoralis [75, 76].

As the number of cancer survivors are increasing with introduction of new anticancer drugs and earlier treatment, cancer-related pain remains an important and challenging issue for oncologists and internists alike. BoNTs, because of their convenience of use (not requiring daily dosing) and generally safe profile, offer a reasonable alternative to strong analgesics. More high-quality studies are needed, however, to better define the role of BoNT therapy in patients with cancer-related pain.

Botulinum Neurotoxin Treatment of End of Life Cancer Pain

The mechanism of focal pain in advanced cancer and end of the life cancer pain is multifactorial. In a majority of patients, pain has a peripheral origin and results from direct invasion of neural tissue by cancer or emanates from the altered and damaged tissue caused by surgery or radiation therapy. Sometimes pain can result from activation of pain mechanisms by a central nervous system cancer that may cause either a neuropathic pain or painful muscle spasms.

The following examples are from the author's experience during his tenure as director of Yale University's Botulinum Toxin Clinic during the years 2004–2015.

Case 4: Severe Jaw Pain and Trismus Due to the Direct Invasion of Masseter Muscle and Jaw Bone by a Non-small Cell Cancer of the Lung

A 69-year-old female with stage IV, non-small cell carcinoma of the lungs with metastasis to bone (femur and petrous bone) and brain underwent multiple courses of chemotherapy and radiation therapy. Three months after completion of radiotherapy, she complained of jaw stiffness, inability to open the mouth fully, and right masseter pain when attempting to open the mouth. Over a few weeks, the problem reached a point where she refrained from eating. Her medications, oxycodone (10 mg, twice daily) and fentanyl (25 mcg patch, every 72 hours), provided temporary pain relief but did not alleviate the trismus. An MRI showed enlargement of the right masseter due to neoplastic involvement (Fig. 18.4). Injection of onabotulinumtoxinA (50 units) into the right masseter and 20 units into the right temporalis decreased the right masseter pain and improved jaw opening for 6 weeks. Subsequent injections of a larger dose of onaA into the right masseter (70 units) with additional injection into the left masseter (30 units) enabled her to eat and improved her quality of life (pain relief, less eating difficulty) over the next 18 months before her demise from complications of cancer.

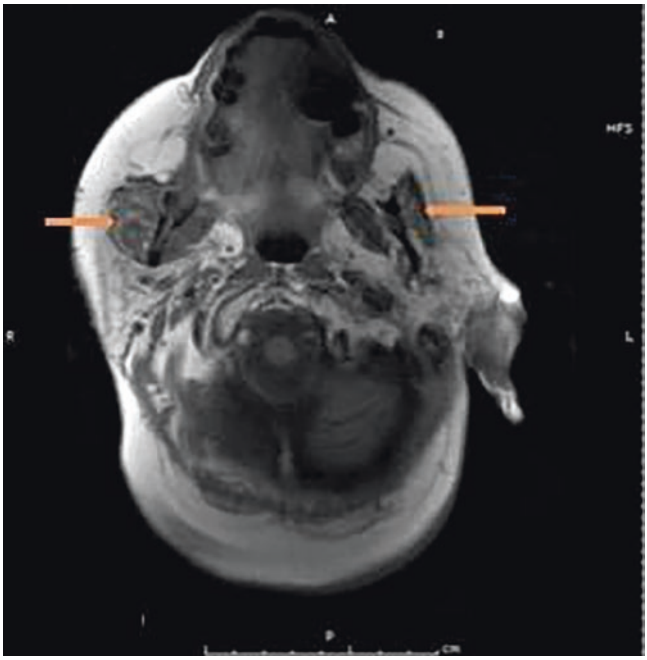

Fig. 18.4 (Case 4). MRI showing an enlarged masseter on the right side probably due to tumor invasion

Case 5: Disabling, Deep Neck and Shoulder Pain Due to an Extensive Pontomedullary Astrocytoma

A 29-year-old male with a grade 3 pontine astrocytoma (Fig. 18.5) experienced painful spasms of neck and shoulder muscles 6 months following radiation therapy. Tizanidine, 2 mg three times a day, had minimal effect, and non-steroidal anti-inflammatory analgesics were not helpful. Abnormal neurological findings included a left 6th and 7th nerve paresis, left-sided spasticity, and gait ataxia. Administration of onabotulinumtoxinA into the neck and shoulder muscles resulted in significant pain relief. The following muscles were injected: left and right splenius capitis (40 units each), left and right trapezius (40 units each), left and right levator scapulae (40 units each), and left and right sternocleidomastoid (20 units each). The total dose was 280 units. Injections were repeated every three months for two years until the patient passed away from complications of cancer.

Case 6: Disabling, Painful and Dystonic Upper Limb Contractions After Gamma Knife Surgery for Recurrent Fronto-Parietal Brain Tumor

A 79-year-old man was referred to the Yale Botulinum Neurotoxin Treatment Clinic for evaluation of painful muscle contractions affecting the left shoulder and left arm muscles. Patient had had recurrent meningiomas in the right posterior frontal region

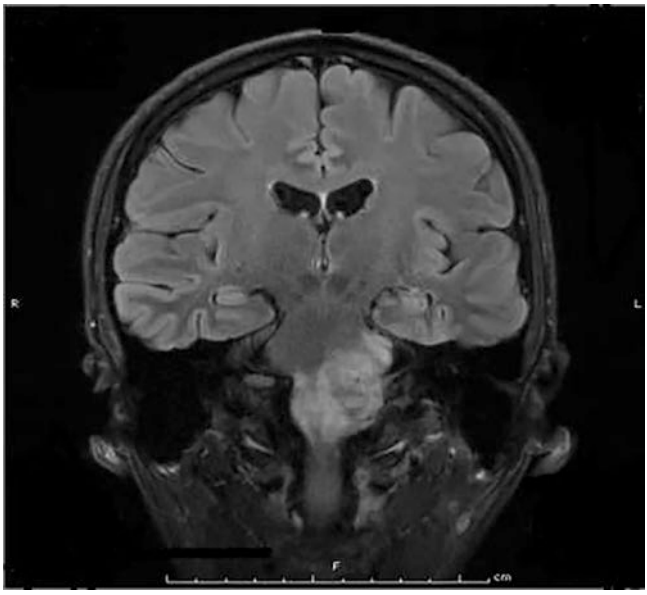

Fig. 18.5 (Case 5): MRI shows a large pontomedullary tumor

for the past several years which had resulted in focal motor seizures of the left side. These seizures were treated with a variety of medications, most recently with a combination of depakote (750 mg daily) and Klonopin (2 mg daily). The recent abnormal movements, however, had begun three months ago shortly following a Gamma Knife surgical excision of a recurrent right posterior frontal lobe tumor. The movements were different from those associated with his seizures in that they occurred as episodic "very painful" contractions of the left upper limb muscles associated with "wandering movements" of that limb. These painful contractions failed to respond to non-opioid analgesics and to baclofen10 mg three times daily

On examination, the patient had a mild left hemiparesis. Several episodes of involuntary movements of the right upper limbs were noted during examination. These were characterized by dystonic posturing of the limb with elbow extension, elbow flexion, arm adduction, and wrist flexion and extension. At times, the affected arm also wandered around aimlessly. These dystonic muscle contractions and postures were painful, unnerved the patient during the day and interfered with his sleep. A magnetic resonance imaging showed areas of edema in the white matter deeper than the posterior frontal mass lesion, possibly related to radiation necrosis from the Gamma Knife procedure (Fig. 18.6). Over the next two years, the patient was treated

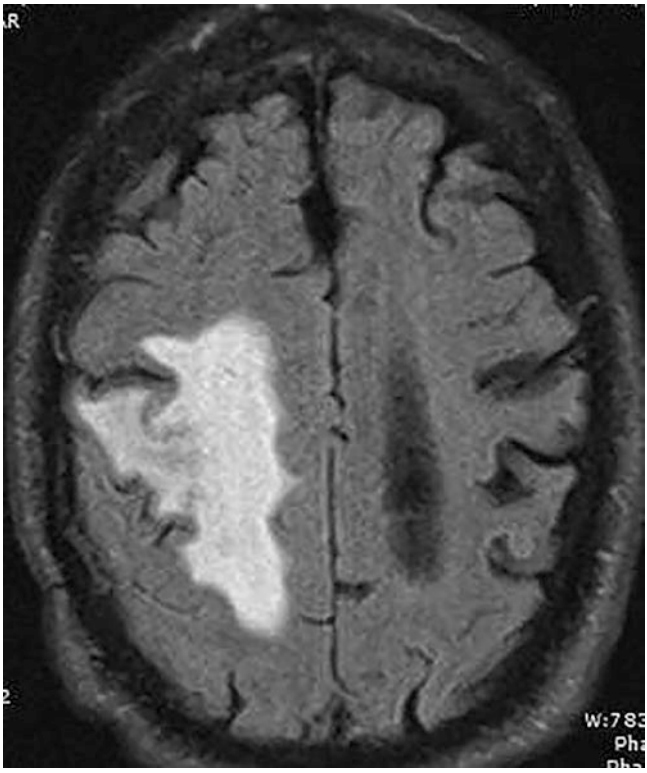

Fig. 18.6 (Case 6): Posterior frontal mass with edema and necrosis partly related to radiation

with intramuscular injections of onabotulinumtoxinA into the left upper limb and shoulder muscles: biceps (100 units), triceps (100 units), pectoralis (100 units), deltoid (40 units), trapezius (60 units), flexor carpi ulnaris (60 units), and flexor carpi radialis (40 units) for a total of 500 units per session. This treatment reduced the frequency of the patient's painful episodic dystonia by 80% as well as lowering the intensity of each episode by 50–70%. BoNT therapy was repeated every 3–4 months. The patient and his wife repeatedly commented on the improvement of his quality of life. The patient died from complications of his brain tumor 2 years after initiation of BoNT therapy.

Comment

The observations illustrated above show that BoNT therapy can provide an avenue for treatment of pain of cancer patients at the end of life. The injections were easy to perform, and treatment had a low and safe side effect profile. In patients with advanced cancer where adding a new medication and extending pain polypharmacy often causes disturbing side effects, BoNT injections every 3–4 months provide a safe and potentially effective alternative to strong analgesic agents. Each of the five patients reported above and their spouses believed the injections improved the patient's quality of life.

References

1. Glare PA, Davies PS, Finlay E, Gulati A, Lemanne D, Moryl N, Oeffinger KC, Paice JA, Stubblefield MD, Syrjala KL. Pain in cancer survivors. J Clin Oncol. 2014;32(16):1739–47. https://doi.org/10.1200/JCO.2013.52.4629. Epub 2014 May 5. PMID: 24799477; PMCID: PMC4031191
2. Schreiber KL, Martel MO, Shnol H, et al. Persistent pain in postmastectomy patients: comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. Pain. 2013;154:660–8.
3. Harrington CB, Hansen JA, Moskowitz M, et al. It's not over when it's over: Long-term symptoms in cancer survivors—a systematic review. Int J Psychiatry Med. 2010;40:163–81.
4. Lam DK, Schmidt BL. Orofacial pain onset predicts transition to head and neck cancer. Pain. 2011;152:1206–9.
5. Stavraka C, Ford A, Ghaem-Maghami S, et al. A study of symptoms described by ovarian cancer survivors. Gynecol Oncol. 2012;125:59–64.
6. Stubblefield MD, Burstein HJ, Burton AW, et al. NCCN task force report: management of neuropathy in cancer. J Natl Compr Canc Netw. 2009;7:S1–S26.
7. Vistad I, Cvancarova M, Kristensen GB, et al. A study of chronic pelvic pain after radiotherapy in survivors of locally advanced cervical cancer. J Cancer Surviv. 2011;5:208–16.
8. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg. 2009;36:170–80.
9. Jensen MP, Chang HY, Lai YH, et al. Pain in long-term breast cancer survivors: frequency, severity, and impact. Pain Med. 2010;11:1099–106.

10. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage. 2016;51(6):1070–-1090.e9. https://doi.org/10.1016/j.jpainsymman.2015.12.340. Epub 2016 Apr 23
11. Kanner RM, Foley KM. Patterns of narcotic drug use in a cancer pain clinic. Ann N Y Acad Sci. 1981;362:161–72.
12. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618–25.
13. List MA, Bilir SP. Functional outcomes in head and neck cancer. Semin Radiat Oncol. 2004;14:178–89.
14. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, Dale O, De Conno F, Fallon M, Hanna M, Haugen DF, Juhl G, King S, Klepstad P, Laugsand EA, Maltoni M, Mercadante S, Nabal M, Pigni A, Radbruch L, Reid C, Sjogren P, Stone PC, Tassinari D, Zeppetella G, European Palliative Care Research Collaborative (EPCRC); European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence based recommendations from the EAPC. Lancet Oncol. 2012;13:e58–68.
15. Harris DG. Management of pain in advanced disease. Br Med Bull. 2014;110:117–28.
16. Borsook D. Neurological diseases and pain. Brain J Neurol. 2012;135(Pt 2):320–44.
17. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manage. 2006;31:58–69.
18. Fisher J, Scott C, Stevens R, Marconi B, Champion L, Freedman GM, Asrari F, Pilepich MV, Gagnon JD, Wong G. Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: radiation therapy oncology group [RTOG] 97–13. Int J Radiat Oncol Biol Phys. 2000;48:1307–10.
19. Kirova YM, Fromantin I, De Rycke Y, Fourquet A, Morvan E, Padiglione S, Falcou MC, Campana F, Bollet MA. Can we decrease the skin reaction in breast cancer patients using hyaluronic acid during radiation therapy- results of phase III randomised trial. Radiother Oncol. 2011;100:205–9.
20. Chargari C, Fromantin I, Kirova YM. Importance of local skin treatments during radiotherapy for prevention and treatment of radio-induced epithelitis. Cancer Radiother. 2009;13:259–66.
21. Fleming JA, O'Connor BD. Use of lidocaine patches for neuropathic pain in a comprehensive cancer center. Pain Res Manag. 2009;14:381–8.
22. Fradkin M, Batash R, Elmaleh S, Debi R, Schaffer P, Schaffer M, Asna N. Management of peripheral neuropathy induced by chemotherapy. Curr Med Chem. 2019;26(25):4698–708. https://doi.org/10.2174/0929867326666190107163756. PMID: 30621553
23. WHO. Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Geneva: World Health Organization; 2018. PMID: 30776210]
24. Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain – an overview of Cochrane reviews. Cochrane Database Syst Rev. 2017;7(7):CD012592. https://doi.org/10.1002/14651858.CD012592.pub2. PMID: 28683172; PMCID: PMC6483487
25. Rock EM, Limebeer CL, Parker LA. Effect of cannabidiolic acid and Δ^9-tetrahydrocannabinol on carrageenan-induced hyperalgesia and edema in a rodent model of inflammatory pain. Psychopharmacology (Berl). 2018;235(11):3259–71. https://doi.org/10.1007/s00213-018-5034-1. Epub 2018 Sep 17. PMID: 30225659.Animal studies
26. Vivanco-Estela AN, Dos-Santos-Pereira M, Guimaraes FS, Del-Bel E, Nascimento GCD. Cannabidiol has therapeutic potential for myofascial pain in female and male parkinsonian rats. Neuropharmacology. 2021;196:108700. https://doi.org/10.1016/j.neuropharm.2021.108700. Epub 2021 Jul 8. PMID: 34246682
27. Moore RA, Fisher E, Finn DP, Finnerup NB, Gilron I, Haroutounian S, Krane E, Rice ASC, Rowbotham M, Wallace M, Eccleston C. Cannabinoids, cannabis, and cannabis-based

medicines for pain management: an overview of systematic reviews. Pain. 2021;162(Suppl 1):S67–79. https://doi.org/10.1097/j.pain.0000000000001941. PMID: 32804833
28. Haroutounian S, Arendt-Nielsen L, Belton J, Blyth FM, Degenhardt L, Di Forti M, Eccleston C, Finn DP, Finnerup NB, Fisher E, Fogarty AE, Gilron I, Hohmann AG, Kalso E, Krane E, Mohiuddin M, Moore RA, Rowbotham M, Soliman N, Wallace M, Zinboonyahgoon N, Rice ASC. International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia: research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management. Pain. 2021;162(Suppl 1):S117–24. https://doi.org/10.1097/j.pain.0000000000002266. PMID: 34138827
29. Nielsen SW, Ruhlmann CH, Eckhoff L, Brønnum D, Herrstedt J, Dalton SO. Cannabis use among Danish patients with cancer: a cross-sectional survey of sociodemographic traits, quality of life, and patient experiences. Support Care Cancer. 2021; https://doi.org/10.1007/s00520-021-06515-z. Epub ahead of print. PMID: 34453567
30. Do EK, Ksinan AJ, Kim SJ, Del Fabbro EG, Fuemmeler BF. Cannabis use among cancer survivors in the United States: analysis of a nationally representative sample. Cancer. 2021;127(21):4040–9. https://doi.org/10.1002/cncr.33794. Epub 2021 Jul 20. PMID: 34387864
31. Rossetto O, Pirazzini M, Fabris F, Montecucco C. Botulinum neurotoxins: mechanism of action. Handb Exp Pharmacol. 2021;263:35–47. https://doi.org/10.1007/164_2020_355. PMID: 32277300
32. Bach-Rojecky L, Relja M, Lacković Z. Botulinum toxin type A in experimental neuropathic pain. J Neural Transm (Vienna). 2005;112(2):215–9. https://doi.org/10.1007/s00702-004-0265-1. PMID: 15657640
33. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017:137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 Jul 1. PMID: 28673722
34. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155(4):674–84. https://doi.org/10.1016/j.pain.2013.12.009. Epub 2013 Dec 11. PMID: 24333775; PMCID: PMC3960322
35. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107(1–2):125–33. https://doi.org/10.1016/j.pain.2003.10.008. PMID: 14715398
36. Mika J, Rojewska E, Makuch W, Korostynski M, Luvisetto S, Marinelli S, Pavone F, Przewlocka B. The effect of botulinum neurotoxin A on sciatic nerve injury-induced neuroimmunological changes in rat dorsal root ganglia and spinal cord. Neuroscience. 2011;175:358–66. https://doi.org/10.1016/j.neuroscience.2010.11.040. Epub 2010 Nov 25. PMID: 21111791
37. Bossowska A, Lepiarczyk E, Mazur U, Janikiewicz P, Markiewicz W. Botulinum toxin type A induces changes in the chemical coding of substance P-immunoreactive dorsal root ganglia sensory neurons supplying the porcine urinary bladder. Toxins (Basel). 2015;7(11):4797–816. https://doi.org/10.3390/toxins7114797. PMID: 26580655; PMCID: PMC4663534
38. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes – an evidence based review. Toxicon. 2018;147:120–8. https://doi.org/10.1016/j.toxicon.2018.01.017. Epub 2018 Feb 1. PMID: 29409817
39. Shin MC, Wakita M, Xie DJ, Yamaga T, Iwata S, Torii Y, Harakawa T, Ginnaga A, Kozaki S, Akaike N. Inhibition of membrane Na+ channels by A type botulinum toxin at femtomolar concentrations in central and peripheral neurons. J Pharmacol Sci. 2012;118(1):33–42. https://doi.org/10.1254/jphs.11060fp. Epub 2011 Dec 10. PMID: 22156364
40. Hong B, Yao L, Ni L, Wang L, Hu X. Antinociceptive effect of botulinum toxin A involves alterations in AMPA receptor expression and glutamate release in spinal dorsal horn neurons. Neuroscience. 2017;357:197–207. https://doi.org/10.1016/j.neuroscience.2017.06.004. Epub 2017 Jun 10. PMID: 28606856

41. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459. PMID: 31387301; PMCID: PMC6723487
42. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012;61(2):236–9. https://doi.org/10.1016/j.neuint.2012.05.001. Epub 2012 May 8. PMID: 22580329
43. Lacković Z. Botulinum toxin and pain. Handb Exp Pharmacol. 2021;263:251–64. https://doi.org/10.1007/164_2019_348. PMID: 32016565
44. Drinovac Vlah V, Filipović B, Bach-Rojecky L, Lacković Z. Role of central versus peripheral opioid system in antinociceptive and anti-inflammatory effect of botulinum toxin type A in trigeminal region. Eur J Pain. 2018;22(3):583–91. https://doi.org/10.1002/ejp.1146. Epub 2017 Nov 13. PMID: 29134730
45. Wang W, Kong M, Dou Y, Xue S, Liu Y, Zhang Y, Chen W, Li Y, Dai X, Meng J, Wang J. Selective expression of a SNARE-cleaving protease in peripheral sensory neurons attenuates pain-related gene transcription and neuropeptide release. Int J Mol Sci. 2021;22(16):8826. https://doi.org/10.3390/ijms22168826. PMID: 34445536; PMCID: PMC8396265
46. Hok P, Veverka T, Hluštík P, Nevrlý M, Kaňovský P. The central effects of botulinum toxin in dystonia and spasticity. Toxins (Basel). 2021;13(2):155. https://doi.org/10.3390/toxins13020155. PMID: 33671128; PMCID: PMC7922085
47. Meng J, Ovsepian SV, Wang J, Pickering M, Sasse A, Aoki KR, Lawrence GW, Dolly JO. Activation of TRPV1 mediates calcitonin gene-related peptide release, which excites trigeminal sensory neurons and is attenuated by a retargeted botulinum toxin with anti-nociceptive potential. J Neurosci. 2009;29(15):4981–92. https://doi.org/10.1523/JNEUROSCI.5490-08.2009. PMID: 19369567; PMCID: PMC6665337
48. Lacković Z. New analgesic: focus on botulinum toxin. Toxicon. 2020;179:1–7. https://doi.org/10.1016/j.toxicon.2020.02.008. Epub 2020 Feb 11. PMID: 32174507
49. Bittencourt da Silva L, Karshenas A, Bach FW, Rasmussen S, Arendt-Nielsen L, Gazerani P. Blockade of glutamate release by botulinum neurotoxin type A in humans: a dermal microdialysis study. Pain Res Manag. 2014;19(3):126–32. https://doi.org/10.1155/2014/410415. PMID: 24851237; PMCID: PMC4158957
50. Meng J, Wang J, Lawrence G, Dolly JO. Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. J Cell Sci. 2007;120(Pt 16):2864–74. https://doi.org/10.1242/jcs.012211. Epub 2007 Jul 31. PMID: 17666428
51. Aoki KR, Francis J. Updates on the antinociceptive mechanism hypothesis of botulinum toxin A. Parkinsonism Relat Disord. 2011;17(Suppl 1):S28–33. https://doi.org/10.1016/j.parkreldis.2011.06.013. PMID: 21999893
52. Van Daele DJ, Finnegan EM, Rodnitzky RL, Zhen W, McCulloch TM, Hoffman HT. Head and neck muscle spasm after radiotherapy: management with botulinum toxin A injection. Arch Otolaryngol Head Neck Surg. 2002;128(8):956–9. https://doi.org/10.1001/archotol.128.8.956. PMID: 12162778
53. Wittekindt C, Liu WC, Preuss SF, Guntinas-Lichius O. Botulinum toxin A for neuropathic pain after neck dissection: a dose-finding study. Laryngoscope. 2006;116:1168–71.
54. Hartl DM, Cohen M, Juliéron M, Marandas P, Janot F, Bourhis J. Botulinum toxin for radiation-induced facial pain and trismus. Otolaryngol Head Neck Surg. 2008;138(4):459–63. https://doi.org/10.1016/j.otohns.2007.12.021. PMID: 18359354
55. Stubblefield MD, Levine A, Custodio CM, Fitzpatrick T. The role of botulinum toxin type A in the radiation fibrosis syndrome: a preliminary report. Arch Phys Med Rehabil. 2008;89(3):417–21. https://doi.org/10.1016/j.apmr.2007.11.022. PMID: 18295617
56. Mittal S, Machado DG, Jabbari B. OnabotulinumtoxinA for treatment of focal cancer pain after surgery and/or radiation. Pain Med. 2012;13:1029–33.
57. Bach CA, Wagner I, Lachiver X, Baujat B, Chabolle F. Botulinum toxin in the treatment of post-radiosurgical neck contracture in head and neck cancer: a novel approach.

Eur Ann Otorhinolaryngol Head Neck Dis. 2012;129(1):6–10. https://doi.org/10.1016/j.anorl.2011.07.002. Epub 2011 Nov 21. PMID: 22104582
58. Rostami R, Mittal SO, Radmand R, Jabbari B. Incobotulinum toxin-A improves post-surgical and post-radiation pain in cancer patients. Toxins (Basel). 2016;8(1):22. https://doi.org/10.3390/toxins8010022. PMID: 26771640; PMCID: PMC4728544
59. De Groef A, Devoogdt N, Van Kampen M, Nevelsteen I, Smeets A, Neven P, Geraerts I, Dams L, Van der Gucht E, Debeer P. Effectiveness of botulinum toxin A for persistent upper limb pain after breast cancer treatment: a double-blinded randomized controlled trial. Arch Phys Med Rehabil. 2018;99(7):1342–51. https://doi.org/10.1016/j.apmr.2017.12.032. Epub 2018 Jan 31. PMID: 29409922
60. De Groef A, Devoogdt N, Van Kampen M, De Hertogh L, Vergote M, Geraerts I, Dams L, Van der Gucht E, Debeer P. The effectiveness of botulinum toxin A for treatment of upper limb impairments and dysfunctions in breast cancer survivors: a randomised controlled trial. Eur J Cancer Care (Engl). 2020;29(1):e13175. https://doi.org/10.1111/ecc.13175. Epub 2019 Sep 30. PMID: 31571329
61. Naik HB, Steinberg SM, Middelton LA, Hewitt SM, Zuo RC, Linehan WM, Kong HH, Cowen EW. Efficacy of intralesional botulinum toxin A for treatment of painful cutaneous leiomyomas: a randomized clinical trial. JAMA Dermatol. 2015;151(10):1096–102. https://doi.org/10.1001/jamadermatol.2015.1793. PMID: 26244563; PMCID: PMC7712636
62. Vuong T, Waschke K, Niazi T, Richard C, Parent J, Liberman S, Mayrand S, Loungnarath R, Stein B, Devic S. The value of botox-A in acute radiation proctitis: results from a phase I/II study using a three-dimensional scoring system. Int J Radiat Oncol Biol Phys. 2011;80(5):1505–11. https://doi.org/10.1016/j.ijrobp.2010.04.017. Epub 2010 Jul 23. PMID: 20656418
63. De Micheli C, Fornengo P, Bosio A, Epifani G, Pascale C. Severe radiation-induced proctitis treated with botulinum anatoxin type A. J Clin Oncol. 2003;21:2627.
64. Potluri TK, Lee FG, Song E, Wallace SJ, Miller N. Use of botulinum toxin A to treat chemotherapy-induced Raynaud's phenomenon. Cureus. 2021;13(1):e12511. https://doi.org/10.7759/cureus.12511. PMID: 33564517; PMCID: PMC7863048
65. 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(17):1473–8. https://doi.org/10.1212/01.wnl.0000345968.05959.cf. Epub 2009 Feb 25. PMID: 19246421
66. 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(12):1827–33. https://doi.org/10.1111/j.1526-4637.2010.01003.x. PMID: 21134121
67. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. Neurology. 2001;56(10):1290–3. https://doi.org/10.1212/wnl.56.10.1290. PMID: 11376175
68. 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(9):649–54. https://doi.org/10.1097/01.phm.0000176339.73591.d7. PMID: 16141740
69. Childers MK, Wilson DJ, Gnatz SM, Conway RR, Sherman AK. Botulinum toxin type A use in piriformis muscle syndrome: a pilot study. Am J Phys Med Rehabil. 2002;81(10):751–9. https://doi.org/10.1097/00002060-200210000-00006. PMID: 12362115
70. Göbel H, Heinze A, Reichel G, Hefter H, Benecke R. Dysport myofascial pain study group. Efficacy and safety of a single botulinum type A toxin complex treatment (Dysport) for the relief of upper back myofascial pain syndrome: results from a randomized double-blind placebo-controlled multicentre study. Pain. 2006;125(1–2):82–8. https://doi.org/10.1016/j.pain.2006.05.001. Epub 2006 Jun 5. PMID: 16750294
71. Dobberfuhl AD, van Uem S, Versi E. Trigone as a diagnostic and therapeutic target for bladder-centric interstitial cystitis/bladder pain syndrome. Int Urogynecol J. 2021; https://doi.org/10.1007/s00192-021-04878-9. Epub ahead of print. PMID: 34156506

72. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, Diener HC, Brin MF. PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6):921–36. https://doi.org/10.1111/j.1526-4610.2010.01678.x. Epub 2010 May 7. PMID: 20487038
73. Aurora SK, Dodick DW, Diener HC, DeGryse RE, Turkel CC, Lipton RB, Silberstein SD. 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(1):61–70. https://doi.org/10.1111/ane.12171. Epub 2013 Sep 20. PMID: 24107267; PMCID: PMC4033567
74. 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(4):915–23. https://doi.org/10.1097/01.AOG.0000237100.29870.cc. PMID: 17012454
75. Layeeque R, Hochberg J, Siegel E, Kunkel K, Kepple J, Henry-Tillman RS, Dunlap M, Seibert J, Klimberg VS. Botulinum toxin infiltration for pain control after mastectomy and expander reconstruction. Ann Surg. 2004; 240(4):608–613; discussion 613–4. doi: 10.1097/01.sla.0000141156.56314.1f. PMID: 15383788; PMCID: PMC1356462
76. Gabriel A, Champaneria MC, Maxwell GP. The efficacy of botulinum toxin A in post-mastectomy breast reconstruction: a pilot study. Aesthet Surg J. 2015;35(4):402–9. https://doi.org/10.1093/asj/sjv040. Epub 2015 Mar 29. PMID: 25825421

Chapter 19
Botulinum Toxin Treatment for Pain Indications in Veterinary Medicine

Introduction

Botulinum neurotoxins can improve pain through different mechanisms. When pain is due to muscle contraction or muscle spasms, the injected toxin relaxes the muscle and hence alleviates pain through blocking the release of acetylcholine from presynaptic vesicles. In the case of neuropathic pain that usually arises from damage to the peripheral sensory nerves innervating skin, muscle, and joints, the mechanism is most likely related to the inhibitory effect of the toxin upon pain modulators and transmitters. It has been shown that botulinum toxins influence the release and function of major pain transmitters (glutamate, substance P, calcitonin gene-related peptide) both peripherally and centrally in animal pain models [1–22].

Some of the other venues through which BoNTs can reduce pain include the toxin's inhibitory function upon sodium channels (important for conducting pain signals) and inhibition of intrafusal muscle fibers after intramuscular injection [23, 24]. By reducing a major sensory input to the spinal cord, the latter can reduce central sensitization [25] which contributes to pain maintenance in chronic pain conditions. In human, botulinum toxins have been shown to improve several pain disorders including chronic migraine; post-herpetic, post-traumatic, and trigeminal neuralgias; and plantar fasciitis, piriformis syndrome, interstitial cystitis, pelvic pain, painful diabetic neuropathy, and certain types of low back pain [26–35].

Chronic pain disorders in dogs and horses are one of the most common medical conditions encountered in veterinary practice. In recent years, some veterinary researchers have explored the analgesic role of botulinum neurotoxins (BoNTs) in painful disorders of dogs and horses. In dogs, the studies have focused on osteoarthritis and post-surgical pain so far. In horses, the analgesic effects of BoNTs have been explored in laminitis, synovitis, and pain in the hoof secondary to degenerative changes of the navicular bone.

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_19

Canine Osteoarthritis

Osteoarthritis is characterized by degeneration of articular cartilage associated with changes in synovial lining and synovial inflammation. The inflammatory response is often mediated by cytokine prostaglandin E2 (PGe2) [36, 37]. A variable prevalence ranging from 2.5 to 20% has been reported in dogs for osteoarthritis [38, 39]. Osteoarthritis is one of the leading causes of canine chronic pain and disability.

Treatment of canine osteoarthritis includes non-pharmacological approaches such as physical therapy, weight bearing physiotherapy, and neutraceuticals. Pharmacological treatment includes oral analgesics as well as intra-articular medicinal injections [40]. Among intra-articular (IA) injections, steroids are commonly employed. IA injection of steroids may alleviate pain, but the results usually do not last more than 8 weeks [41]. Furthermore, IA injection of steroids can cause several side effects such as septic arthritis [42, 43]. Recently, intra-articular slow-release triamcinolone acetonide from polyesteramide microspheres was found helpful in treatment of a cohort of dogs with osteoarthritis [44]. Trials with IA injection of autologous adipose-derived stem cells and plasma-rich platelets are ongoing in canine osteoarthritis with some preliminary results showing improvement of pain and quality of life up to 6 months [45, 46].

Botulinum Toxin Treatment of Osteoarthritis in Dogs

One open-label and two, double-blind, placebo-controlled studies have reported on the efficacy of IA BoNT injections in dogs [47–49] (Table 19.1).

In 2004, Hadley et al. [47] reported the result of a pilot, open-label study on the efficacy of IA injections of BoNT-A in five dogs with osteoarthritis. All dogs had chronic pain and their condition was stable on non-steroidal anti-inflammatory drugs and neuraceuticals (glucosamine/chondroitin, vitamin E, fish oil). The studied dogs had lameness and pain due to elbow or hip osteoarthritis. After sedation, each dog received an IA injection of 25 units of onabotulinumtoxinA. Animals were evaluated by pressure platform gait analysis (ground pressure/weight bearing) and owner perception of outcome (locomotion and discomfort) at baseline and at 2, 4, 8, and 12 weeks post-injection. All dogs, following onA injection, demonstrated improvement of ground reaction forces. At week 12, two of five owners reported significant, and one reported moderate improvement of dogs' function and discomfort. Among the other two, one owner reported mild, and the other reported no improvement. No side effects were noted.

In 2014, Heikkila et al. [48] published on the results of their study on BoNT-A's effectiveness in osteoarthritis of 35 client-owned dogs. The animals had osteoarthritis of the stifle, hip, and elbow joints. The study was double-blind and placebo-controlled. Each dog received intra-articular injection (into painful joint) of either onabotulinumtoxinA (Botox) or placebo (saline). The toxin dose was 30 units. The

Table 19.1 Studies assessing efficacy of BoNT injections in canine osteoarthritis

Authors and date	Type of study	Study class	Number of dogs	Location of OA	Toxin type	Dose in units	Assessed scales	Results
Hadley et al. [47]	Open label	IV	5	Elbow, hip	onaA	25	Pressure platform gait analysis (PPGA), owner perception (OP)	PPGA improved in all dogs at week 12, OP: two dogs significantly and one dog moderately improved
Heikkila et al. [48]	Double-blind, placebo-controlled	I	35	Stifle, elbow, hip	onaA	30	Helsinki Chronic Pain Index (HCPI), Ground Reaction Force (GRF)	At 12 weeks, both HCPI and GRF improved significantly ($P < 0.005$)
Nicacio et al. [49]	Double-blind, placebo-controlled	II	16	Hip	aboA	25	Vet-score, Helsinki Chronic Pain Index (HCPI)	Both toxin and placebo groups have improved in all measures compared to baseline. The effect was higher in the placebo group

onaA onabotulinumtoxinA (Botox), *aboA* abobotulinumtoxinA (Dysport), *PPGA* Pressure Platform Gait Analysis, *HCPI* Helsinki Chronic Pain Index, *GRF* Ground Reaction Force, *CBPI* Canine Brief Pain Inventory, *OA* osteoarthritis

primary outcomes of the study were Helsinki Chronic Pain Index (HCPI) and changes in the ground reaction forces evaluated by force plate. HCPI is a questionnaire for dog owners through which they rate a dog's chronic orthopedic pain. In this scale, a score of 17 or higher denotes severe pain. Secondary outcomes of the study consisted of the need for rescue analgesia and a subjective pain scale rated by a veterinarian. Dog owners were given Carprofen tablets (Rimadyl of Pfizer) to be given to the dog once daily (4 mg/Kg) if needed. They would record this rescue analgesic as 0 = not needed, 1 = needed once or twice/week, 2 = needed three to four times/week, 3 = needed five to six times/week, and 5 = when needed every day. The duration of the study was 12 weeks. At the end of the study (12 weeks post-injection), the investigators noted a significant improvement of ground force in the toxin injected group ($P < 0.005$). The toxin group also demonstrated a significant reduction of HCPI score (pain score) from baseline when compared to placebo. The authors stated that none of the participant dogs in the study had serious side effects.

In 2019, another study by Nicasio et al. [49] was published on the issue of BoNT treatment of canine osteoarthritis. In this double-blind, placebo-controlled investigation, the researchers injected either abobotulinumtoxinA (aboA-Dysport) or saline into the arthritic hip joint of 16 dogs with osteoarthritis. The injected dose of aboA was 25 units. The hip joints were affected by hip dysplasia. The dogs' response to intra-articular (IA) toxin injections was evaluated over 12 weeks with a Vet-score and an owner rating scale. The Vet-score includes four subsets of pain on manipulation, lameness, ability to jump, and ability to climb stairs, each rated from 1 to 4. The owners were trained to use two validated pain scales to rate the level of pain change in the dogs, namely, HCPI and Canine Brief Pain Inventory (CBPI). The investigators found that both aboA and saline injections improved Vet Scores, HCPI, and CBPI scores significantly, but the improvement had a higher magnitude in the saline group.

Comment

Using the efficacy criteria of Assessment and Guideline subcommittee of the American Academy of Neurology [50, 51], IA injections of onabotulinumtoxinA for canine osteoarthritis would have a level B efficacy (probably effective based on one class I study [48]). The negative class II study of Nicacio et al. [49] has a large placebo effect that makes determination of efficacy not possible. Furthermore, if one uses a ratio of 1:2.5 for onaA/aboA, the dose used in this study [49] would be substantially lower (almost half) than the toxin dose used in the study of Heikkila et al. [48].

In a double-blind, placebo-controlled study, Heikkila et al. [52] investigated the effect of IA BoNT injections in healthy dogs. Six dogs were injected either by 30 units of onaA or saline (contralateral joint). The authors reported no clinical, cytological, and histological adverse effects. There was electrophysiological evidence of toxin spread to the adjacent joint muscles, but they noted no clinically detectable weakness.

BoNT Injections for Post-surgical Pain in Dogs

In human, a growing number of publications have demonstrated efficacy of BoNT injections in relieving post-surgical neck and head pain, post-mastectomy pain, and pain after breast expander surgery [53–56]. In dogs, one study has reported the results of BoNT therapy in post-mastectomy pain. Vilhegas et al. [57] studied the analgesic effect of BoNT-A injections in dogs scheduled to have bilateral mastectomy for malignant tumors. The study was double-blind, placebo-controlled and had a duration of 10–14 days. Investigators enrolled 16 dogs with breast malignancy who were planned to have bilateral mastectomy. The study cohort was randomized

into toxin and placebo groups. The dogs in the toxin group were injected with abobotulinumtoxinA (7 units/kg), 24 h before surgery. Injections were performed into the middle of the mammary glands. Same volume of normal saline was injected into the breast of the control group. Authors assessed dogs' post-operative pain by visual analog scale (VAS, scale of 0–10) and by modified Glasgow Composite Measure Pain Scale (GCMPS). Rescue analgesia was prescribed during the study when deemed necessary. The authors found that pain scores assessed by VAS and modified GCMPS were significantly lower in the BoNT-A group compared to the control group ($P < 0.05$). This pain reduction was noted from 8 h to 60 h and from 12 h to 60 h post-injection, respectively, after extubation. Significantly more rescue analgesia had to be used by more dogs in the control group (7/8) compared with the dogs in the BoNT-A group (2/8) ($P = 0.022$). The authors concluded that "pre-emptive BoNT-A therapy appears to be effective as an adjuvant for postoperative pain management in dogs undergoing bilateral radical mastectomy." No adverse effects were noted during this study after BoNT injections into the dogs' breasts.

BoNT Treatment in Equine Pain Disorders

Horses may suffer several ailments that cause chronic pain, leading to lameness and loss of function. The literature on the use of BoNTs as an analgesic in equine pain disorders is limited to studies on laminitis, synovitis, and chronic pain in the hoof due to degeneration of navicular bone and the surrounding tissue.

Laminitis

Laminitis refers to inflammation of the soft tissue structures that attach the coffin (pedal bone of the foot) to the hoof wall. Inflammation and damage to the laminae of the horse can cause severe pain and lead to instability of the coffin bone in the hoof. With the progression of the disorder, the third phalanx rotates and undergoes distal displacement in the hoof capsule. In more severe cases, it can lead to complete separation and rotation of the pedal bone within the hoof wall. Recurrent attacks of laminitis after an initial attack are not uncommon. Severe laminitis can cripple the horse and may even be fatal. Since management of laminitis is difficult, prevention of laminitis is an important task in equine veterinary medicine.

A variable incidence of 1.5–24% has been reported for laminitis that reflects variation in the type of horse, its nutritional status, and its geographical location [58]. Mitchell et al. [59] define five principles for treatment of acute equine laminitis: nutritional and medical management of primary disease process, cryotherapy (keeping the temperature below 10 degrees centigrade for 48 h), anti-inflammatory therapy, pain control, and biomechanical optimization. Among non-steroidal

anti-inflammatory drugs, phenylbutazone is commonly used with a dose of 2.2–4.4 mg/kg given by mouth or administered intravenously every 12 h [59].

For management of mild to moderate pain, amitriptyline and soluble epoxide hydrolase inhibitor may be helpful [60]. More severe cases of pain may require use of opioids or constant rate infusions of α-2 agonists, ketamine, and lidocaine [60]. In case of recalcitrant pain, deep digital tendon tenotomy may offer pain relief [61].

Botulinum Toxin Treatment in Equine Laminitis

The feasibility of denervating the deep digital flexors of the horse by BoNT injections (producing a similar effect to tenotomy) has been explored by several studies in recent years [62–64]. These studies have shown that injections of BoNTs into the deep digital flexors produce sustained denervation of these muscles with reduced EMG activity and, in appropriate doses, do not cause lameness or loss of function. The authors concluded that BoNT injections may offer a safe approach for treatment of laminitis, the efficacy of which needs to be confirmed by clinical trials.

In a small open-label study, Carter and Renroe [65] investigated the effect of deep digital flexor denervation by BoNT-A for treatment of equine laminitis. Seven horses with chronic laminitis were injected by 100–200 units of onabobotulinumtoxinA (Botox) into the digital flexors of one or both front limbs. The horses were followed for a period of 6 to 36 months. Six of the seven horses demonstrated improvement of pain and function, most of them becoming pressure sound. One of the six responding horses fully recovered and could ride all gaits. No adverse effects were seen after BoNT injections.

Botulinum Toxin Effect on Podotrochlear (Navicular) Pain Syndrome

In the horse's hoof, podotrochlear apparatus (navicular apparatus) includes the navicular bone, the navicular bursa, the coffin joint, and suspensory ligament of the navicular bone as well as the deep digital flexor tendon (DDFT). Degenerative changes affecting navicular bone and adjacent tissue result in hoof pain and lameness. Corrective shoeing, controlled exercises, extracorporeal shock therapy as well as oral or intra-articular injection of anti-inflammatory drugs are helpful, but still a majority of the horses fail to respond to these treatments [66].

In an open-label study [66], the authors injected rimabotulinumtoxinB (Myobloc) into the navicular bursa of seven horses with severe lameness and pain due to degeneration of podonavicular apparatus. The dose of injected toxin was 3.8–4.5 units/kg. The response to BoNT-B injections was assessed over 14 days via study of videos by veterinarians. After BoNT-B injections, investigators noted significant decrease

in the severity of lameness. However, none of the horses fully recovered from lameness which the authors attributed to possible low dose of the injected toxin.

BoNT Effect on Acute Synovitis

Depuy et al. [67], in a double-blind, placebo-controlled study, injected 50 units of onabotulinumtoxinA into the middle carpal joint (both limbs) of two healthy horses. Two other horses (controls) received the same volume of saline injections bilaterally. Then, all four horses were injected by interleukin 1-beta in order to induce acute synovitis. Study veterinarians evaluated the antinociceptive activity of the injected BoNT using a computer-assisted analysis of lameness. After interleukin injection, both saline-injected horses developed lameness, whereas only one of the two horses that had received BoNT injection demonstrated lameness. Following euthanasia at day 14 post-interleukin injection, the histological evaluation of the injected joints revealed evidence of suppurative inflammation in all four horses.

Comment

The low-quality studies cited above suggest an antinociceptive role for BoNTs in certain equine pain disorders. The proof of utility of BoNTs in equine pain disorders awaits the results of well-designed blinded and placebo-controlled studies. Since horses are known to be more sensitive than many other species (including man) to the effects of botulinum toxins [68], future studies need to monitor and titrate the injected doses carefully in order to avoid inducing botulism. A detailed and up-to-date review of BoNT toxin treatment in veterinary medicine has been recently published by Helga Heikkila PhD, DVM in 2020 [69].

References

1. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the antinociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;358:137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 Jul 1. PMID: 28673722
2. Rossetto O, Pirazzini M, Fabris F, Montecucco C. Botulinum neurotoxins: mechanism of action. Handb Exp Pharmacol. 2021;263:35–47. https://doi.org/10.1007/164_2020_355. PMID: 32277300
3. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155(4):674–84. https://doi.org/10.1016/j.pain.2013.12.009. Epub 2013 Dec 11. PMID: 24333775; PMCID: PMC3960322

4. Bach-Rojecky L, Relja M, Lacković Z. Botulinum toxin type A in experimental neuropathic pain. J Neural Transm (Vienna). 2005;112(2):215–9. https://doi.org/10.1007/s00702-004-0265-1. PMID: 15657640
5. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004;107(1–2):125–33. https://doi.org/10.1016/j.pain.2003.10.008. PMID: 14715398
6. Mika J, Rojewska E, Makuch W, Korostynski M, Luvisetto S, Marinelli S, Pavone F, Przewlocka B. The effect of botulinum neurotoxin A on sciatic nerve injury-induced neuroimmunological changes in rat dorsal root ganglia and spinal cord. Neuroscience. 2011;175:358–66. https://doi.org/10.1016/j.neuroscience.2010.11.040. Epub 2010 Nov 25. PMID: 21111791
7. Bossowska A, Lepiarczyk E, Mazur U, Janikiewicz P, Markiewicz W. Botulinum toxin type A induces changes in the chemical coding of substance P-immunoreactive dorsal root ganglia sensory neurons supplying the porcine urinary bladder. Toxins (Basel). 2015;7(11):4797–816. https://doi.org/10.3390/toxins7114797. PMID: 26580655; PMCID: PMC4663534
8. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes -an evidence based review. Toxicon. 2018;147:120–8. https://doi.org/10.1016/j.toxicon.2018.01.017. Epub 2018 Feb 1. PMID: 29409817
9. Shin MC, Wakita M, Xie DJ, Yamaga T, Iwata S, Torii Y, Harakawa T, Ginnaga A, Kozaki S, Akaike N. Inhibition of membrane Na+ channels by A type botulinum toxin at femtomolar concentrations in central and peripheral neurons. J Pharmacol Sci. 2012;118(1):33–42. https://doi.org/10.1254/jphs.11060fp. Epub 2011 Dec 10. PMID: 22156364
10. Hong B, Yao L, Ni L, Wang L, Hu X. Antinociceptive effect of botulinum toxin A involves alterations in AMPA receptor expression and glutamate release in spinal dorsal horn neurons. Neuroscience. 2017;357:197–207. https://doi.org/10.1016/j.neuroscience.2017.06.004. Epub 2017 Jun 10. PMID: 28606856
11. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11(8):459. https://doi.org/10.3390/toxins11080459. PMID: 31387301; PMCID: PMC6723487
12. Lacković Z. Botulinum toxin and pain. Handb Exp Pharmacol. 2021;263:251–64. https://doi.org/10.1007/164_2019_348. PMID: 32016565
13. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012;61(2):236–9. https://doi.org/10.1016/j.neuint.2012.05.001. Epub 2012 May 8. PMID: 22580329
14. Drinovac Vlah V, Filipović B, Bach-Rojecky L, Lacković Z. Role of central versus peripheral opioid system in antinociceptive and anti-inflammatory effect of botulinum toxin type A in trigeminal region. Eur J Pain. 2018;22(3):583–91. https://doi.org/10.1002/ejp.1146. Epub 2017 Nov 13. PMID: 29134730
15. Wang W, Kong M, Dou Y, Xue S, Liu Y, Zhang Y, Chen W, Li Y, Dai X, Meng J, Wang J. Selective expression of a SNARE-cleaving protease in peripheral sensory neurons attenuates pain-related gene transcription and neuropeptide release. Int J Mol Sci. 2021;22(16):8826. https://doi.org/10.3390/ijms22168826. PMID: 34445536; PMCID: PMC8396265
16. Hok P, Veverka T, Hluštík P, Nevrlý M, Kaňovský P. The central effects of botulinum toxin in dystonia and spasticity. Toxins (Basel). 2021;13(2):155. https://doi.org/10.3390/toxins13020155. PMID: 33671128; PMCID: PMC7922085
17. Meng J, Ovsepian SV, Wang J, Pickering M, Sasse A, Aoki KR, Lawrence GW, Dolly JO. Activation of TRPV1 mediates calcitonin gene-related peptide release, which excites trigeminal sensory neurons and is attenuated by a retargeted botulinum toxin with anti-nociceptive potential. J Neurosci. 2009;29(15):4981–92. https://doi.org/10.1523/JNEUROSCI.5490-08.2009. PMID: 19369567; PMCID: PMC6665337
18. Li X, Ye Y, Zhou W, Shi Q, Wang L, Li T. Anti-inflammatory effects of BoNT/a against complete Freund's adjuvant-induced arthritis pain in rats: transcriptome analysis. Front Pharmacol. 2021;12:735075. https://doi.org/10.3389/fphar.2021.735075. PMID: 34803684; PMCID: PMC8602683

19. Lacković Z. New analgesic: focus on botulinum toxin. Toxicon. 2020;179:1–7. https://doi.org/10.1016/j.toxicon.2020.02.008. Epub 2020 Feb 11. PMID: 32174507
20. Meng J, Wang J, Lawrence G, Dolly JO. Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. J Cell Sci. 2007;120(Pt 16):2864–74. https://doi.org/10.1242/jcs.012211. Epub 2007 Jul 31. PMID: 17666428
21. Waskitho A, Yamamoto Y, Raman S, Kano F, Yan H, Raju R, Afroz S, Morita T, Ikutame D, Okura K, Oshima M, Yamamoto A, Baba O, Matsuka Y. Peripherally administered botulinum toxin type A localizes bilaterally in trigeminal ganglia of animal model. Toxins (Basel). 2021;13(10):704. https://doi.org/10.3390/toxins13100704. PMID: 34678997; PMCID: PMC8541196
22. Vacca V, Marinelli S, Eleuteri C, Luvisetto S, Pavone F. Botulinum neurotoxin a enhances the analgesic effects on inflammatory pain and antagonizes tolerance induced by morphine in mice. Brain Behav Immun. 2012;26(3):489–99. https://doi.org/10.1016/j.bbi.2012.01.002. Epub 2012 Jan 20. PMID: 22281280. Appl Microbiol Biotechnol
23. Shin MC, Wakita M, Xie DJ, Yamaga T, Iwata S, Torii Y, Harakawa T, Ginnaga A, Kozaki S, Akaike N. Inhibition of membrane Na+ channels by A type botulinum toxin at femtomolar concentrations in central and peripheral neurons. J Pharmacol Sci. 2012;118(1):33–42. https://doi.org/10.1254/jphs.11060fp. Epub 2011 Dec 10. PMID: 22156364
24. Rosales RL, Arimura K, Takenaga S, Osame M. Extrafusal and intrafusal muscle effects in experimental botulinum toxin-A injection. Muscle Nerve. 1996;19(4):488–96. https://doi.org/10.1002/(SICI)1097-4598(199604)19:4<488::AID-MUS9>3.0.CO;2-8. PMID: 8622728
25. Aoki KR, Francis J. Updates on the antinociceptive mechanism hypothesis of botulinum toxin a. Parkinsonism Relat Disord. 2011;17(Suppl 1):S28–33. https://doi.org/10.1016/j.parkreldis.2011.06.013. PMID: 21999893
26. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, Diener HC, Brin MF. PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6):921–36. https://doi.org/10.1111/j.1526-4610.2010.01678.x. Epub 2010 May 7. PMID: 20487038
27. Wu CJ, Lian YJ, Zheng YK, Zhang HF, Chen Y, Xie NC, Wang LJ. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32(6):443–50. https://doi.org/10.1177/0333102412441721. Epub 2012 Apr 5. PMID: 22492424
28. 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(12):1827–33. https://doi.org/10.1111/j.1526-4637.2010.01003.x. PMID: 21134121
29. 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(17):1473–8. https://doi.org/10.1212/01.wnl.0000345968.05959.cf. Epub 2009 Feb 25. PMID: 19246421
30. 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(9):649–54. https://doi.org/10.1097/01.phm.0000176339.73591.d7. PMID: 16141740
31. Childers MK, Wilson DJ, Gnatz SM, Conway RR, Sherman AK. Botulinum toxin type A use in piriformis muscle syndrome: a pilot study. Am J Phys Med Rehabil. 2002;81(10):751–9. https://doi.org/10.1097/00002060-200210000-00006. PMID: 12362115
32. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. Neurology. 2001;56(10):1290–3. https://doi.org/10.1212/wnl.56.10.1290. PMID: 11376175
33. Giannantoni A, Gubbiotti M, Bini V. Botulinum neurotoxin a intravesical injections in interstitial cystitis/bladder painful syndrome: a systematic review with meta-analysis. Toxins

(Basel). 2019;11(9):510. https://doi.org/10.3390/toxins11090510. PMID: 31480323; PMCID: PMC6784147
34. 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(4):915–23. https://doi.org/10.1097/01.AOG.0000237100.29870.cc. PMID: 17012454
35. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol. 2008;64(3):274–83. https://doi.org/10.1002/ana.21427. Erratum in: Ann Neurol. 2009 Mar;65(3):359. PMID: 18546285
36. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, Carr AJ. Osteoarthritis Lancet. 2015;386:376–87. https://doi.org/10.1016/S0140-6736(14)60802-3. [PubMed]
37. Hugle T, Geurts J. What drives osteoarthritis? - Synovial versus subchondral bone pathology. Rheumatology. 2017;56:1461–71.
38. Johnston SA. Osteoarthritis. Joint anatomy, physiology, and pathobiology. Vet Clin North Am Small Anim Pract. 1997;27(4):699–723. https://doi.org/10.1016/s0195-5616(97)50076-3. PMID: 9243777
39. Anderson KL, O'Neill DG, Brodbelt DC, Church DB, Meeson RL, Sargan D, Summers JF, Zulch H, Collins LM. Prevalence, duration and risk factors for appendicular osteoarthritis in a UK dog population under primary veterinary care. Sci Rep. 2018;8(1):5641. https://doi.org/10.1038/s41598-018-23940-z. PMID: 29618832; PMCID: PMC5884849
40. Heikkila H. Chapter 17, Botulinum toxin treatment in veterinary medicine: clinical implications. In: Jabbari B, editor. Botulinum toxin treatment in surgery, dentistry and veterinary medicine. Switzerland: Springer; 2020. p. 337–57.
41. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006;2:CD005328.
42. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, Zink A, Buttgereit F. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009;68:1119–24. https://doi.org/10.1136/ard.2008.092163.
43. Xing D, Yang Y, Ma X, Ma J, Ma B, Chen Y. Dose intraarticular steroid injection increase the rate of infection in subsequent arthroplasty: grading the evidence through a meta-analysis. J Orthop Surg Res. 2014;9:107-014-0107-2. https://doi.org/10.1186/s13018-014-0107-2.
44. Tellegen A, Beukers M, Rudnik-Jansen I, et al. Intra-articular slow-release triamcinolone acetonide from polyesteramide microspheres as a treatment for osteoarthritis. Pharmaceutics. 2021;13(3):372. https://doi.org/10.3390/pharmaceutics13030372. Published 2021 Mar 11
45. Sanghani-Kerai A, Black C, Cheng SO, Collins L, Schneider N, Blunn G, Watson F, Fitzpatrick N. Clinical outcomes following intra-articular injection of autologous adipose-derived mesenchymal stem cells for the treatment of osteoarthritis in dogs characterized by weight-bearing asymmetry. Bone Joint Res. 2021;10:650–8. https://doi.org/10.1302/2046-3758.1010.BJR-2020-0540.R1. PMID: 34628940; PMCID: PMC8559970
46. Alves JC, Santos A, Jorge P. Platelet-rich plasma therapy in dogs with bilateral hip osteoarthritis. BMC Vet Res. 2021;17(1):207. https://doi.org/10.1186/s12917-021-02913-x. PMID: 34090433; PMCID: PMC8180029
47. Hadley HS, Wheeler JL, Petersen SW. Effects of intra-articular botulinum toxin type A (Botox) in dogs with chronic osteoarthritis. Vet Comp Orthop Traumatol. 2010;23(4):254–8. https://doi.org/10.3415/VCOT-09-07-0076. Epub 2010 Jun 21. PMID: 20585713
48. Heikkilä HM, Hielm-Björkman AK, Morelius M, Larsen S, Honkavaara J, Innes JF, Laitinen-Vapaavuori OM. Intra-articular botulinum toxin A for the treatment of osteoarthritic joint pain in dogs: a randomized, double-blinded, placebo-controlled clinical trial. Vet J. 2014;200(1):162–9. https://doi.org/10.1016/j.tvjl.2014.01.020. Epub 2014 Feb 5. PMID: 24675370
49. Nicácio GM, Luna SPL, Cavaleti P, Cassu RN. Intra-articular botulinum toxin A (BoNT/A) for pain management in dogs with osteoarthritis secondary to hip dysplasia: A randomized con-

trolled clinical trial. J Vet Med Sci. 2019;81(3):411–7. https://doi.org/10.1292/jvms.18-0506. Epub 2019 Jan 15. PMID: 30643103; PMCID: PMC6451911
50. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008;71(20):1634–8. https://doi.org/10.1212/01.wnl.0000336533.19610.1b. PMID: 19001254
51. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology. 2008;71(20):1639–43. https://doi.org/10.1212/01.wnl.0000336535.27773.c0. PMID: 19001255
52. Heikkilä HM, Jokinen TS, Syrjä P, Junnila J, Hielm-Björkman A, Laitinen-Vapaavuori O. Assessing adverse effects of intra-articular botulinum toxin A in healthy Beagle dogs: a placebo-controlled, blinded, randomized trial. PLoS One. 2018;13(1):e0191043. https://doi.org/10.1371/journal.pone.0191043. PMID: 29320549; PMCID: PMC5761897
53. Alvandipour M, Tavallaei M, Rezaei F, Khodabakhsh H. Postoperative outcomes of intra-sphincteric botox injection during hemorrhoidectomy: a double-blind clinical trial. J Res Med Sci. 2021;26:53. https://doi.org/10.4103/jrms.JRMS_612_18. PMID: 34729061; PMCID: PMC8506240
54. Blaha L, Chouliaras K, White A, McNatt S, Westcott C. Intraoperative botulinum toxin Chemodenervation and analgesia in Abdominal Wall reconstruction. Surg Innov. 2020;24:1553350620975253. https://doi.org/10.1177/1553350620975253. Epub ahead of print. PMID: 33234030
55. Shandilya S, Mohanty S, Sharma P, Chaudhary Z, Kohli S, Kumar RD. Effect of preoperative intramuscular injection of botulinum toxin a on pain and mouth opening after surgical intervention in temporomandibular joint Ankylosis cases: a controlled clinical trial. J Oral Maxillofac Surg. 2020;78(6):916–26. https://doi.org/10.1016/j.joms.2020.02.011. Epub 2020 Feb 19. PMID: 32171600
56. Gabriel A, Champaneria MC, Maxwell GP. The efficacy of botulinum toxin a in post-mastectomy breast reconstruction: a pilot study. Aesthet Surg J. 2015;35(4):402–9. https://doi.org/10.1093/asj/sjv040. Epub 2015 Mar 29. PMID: 25825421
57. Vilhegas S, Cassu RN, Barbero RC, Crociolli GC, Rocha TL, Gomes DR. Botulinum toxin type A as an adjunct in postoperative pain management in dogs undergoing radical mastectomy. Vet Rec. 2015;177(15):391. https://doi.org/10.1136/vr.102993. Epub 2015 Oct 7. PMID: 26446882
58. Wylie CE, Collins SN, Verheyen KL, Richard NJ. Frequency of equine laminitis: a systematic review with quality appraisal of published evidence. Vet J. 2011;189(3):248–56. https://doi.org/10.1016/j.tvjl.2011.04.014. Epub 2011 Jun 12. PMID: 21665498
59. Mitchell CF, Fugler LA, Eades SC. The management of equine acute laminitis. Vet Med (Auckl). 2014;6:39–47. https://doi.org/10.2147/VMRR.S39967. PMID: 30101095; PMCID: PMC6067769
60. Hopster K, Driessen B. Pharmacology of the equine foot: medical pain management for laminitis. Vet Clin North Am Equine Pract. 2021;37(3):549–61. https://doi.org/10.1016/j.cveq.2021.08.004. Epub 2021 Oct 19. PMID: 34674911
61. Eastman TG, Honnas CM, Hague BA, Moyer W, von der Rosen HD. Deep digital flexor tenotomy as a treatment for chronic laminitis in horses: 35 cases (1988–1997). J Am Vet Med Assoc. 1999;214(4):517–9. Erratum in: J Am Vet Med Assoc 1999 Apr 15;214(8):1217. PMID: 10029854
62. Hardeman LC, van der Meij BR, Oosterlinck M, Veraa S, van der Kolk JH, Wijnberg ID, et al. Effect of Clostridium botulinum toxin type A injections into the deep digital flexor muscle on the range of motion of the metacarpus and carpus, and the force distribution underneath the hooves, of sound horses at the walk. Vet J. 2013;198:e152–6.
63. Wijnberg ID, Hardeman LC, van der Meij BR, Veraa S, Back W, van der Kolk JH. The effect of Clostridium botulinum toxin type A injections on motor unit activity of the deep digital flexor muscle in healthy sound Royal Dutch sport horses. Vet J. 2013;1(198):e147–51.

64. Hardeman LC, van der Meij BR, Back W, van der Kolk JH, Wijnberg ID. The use of electromyography interference pattern analysis to determine muscle force of the deep digital flexor muscle in healthy and laminitic horses. Vet Q. 2015;36(1):10–5.
65. Carter DW, Renfroe BJ. A novel approach to the treatment and prevention of laminitis:botulinum toxin type a for the treatment of laminitis. J Equine Vet. 2009;29(7):595–600.
66. Nibeyro SDG, White Na II, Wepy NM. Outcome of medical treatment for horses with foot pain: 56 cases. Equine Vet J. 2010;42(8):680–5.
67. DePuy T, Howard R, Keegan K, Wilson D, Kramer J, Cook JL, et al. Effects of intra-articular botulinum toxin type A in an equine model of acute synovitis: a pilot study. Am J Phys Med Rehabil. 2007;86(10):777–83.
68. Bakheit AM, Ward CD, McLellan DL. Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: a report of two cases. J Neurol Neurosurg Psychiatry. 1997;62(2):198. https://doi.org/10.1136/jnnp.62.2.198. PMID: 9048725; PMCID: PMC486736
69. Helga Heikkila. Chapter 17. In: Bahman Jabbari, editor. Botulinum toxin treatment in surgery, dentistry and veterinary medicine. Cham: Springer; 2020. p. 337–357.

Chapter 20
Future Prospects of Pain Treatment with Botulinum Neurotoxins

Introduction

Botulinum neurotoxins (BoNT) have been shown to inhibit the release of pain mediators and pain transmitters such as glutamate, calcitonin gene-related peptide, and substance P from sensory nerve endings and sensory neurons [1–15]. BoNT-A is already widely used in clinical practice for treatment of chronic migraine. Small blinded studies have also demonstrated the efficacy of all three commonly used BoNTs (ona, abo, and inco) in several neuropathic pain disorders paving the way for larger clinical trials in this area (Chaps. 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19 of this book).

It has been known for years that BoNTs block the release of acetylcholine in neuromuscular junction via targeting synaptic SNARE proteins [16]. In recent years, investigators have shown that SNARE proteins are also expressed on the surface of the peripheral and central sensory neurons [17]. The antinociceptive effect of BoNT injections in human pain disorders, as described in Chaps. 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19 of this book, can be partly related to the toxins effect on sensory neurons. Further published data indicates that peripherally injected BoNTs reach the central nervous system through retrograde transmission and in the central nervous system the cleaved SNAP 25 (SNARE protein targeted by type A toxins) is able to move from one cell to another via transcytosis [18–20].

In the past few years, a consorted effort by basic scientists and neurotoxicologists focused on developing toxin molecules that can specifically target sensory neurons and/or specific nociceptive sensory receptors. Such products have the potential to enhance the antinociceptive activity of the toxin and, theoretically, do not affect the neuromuscular junction. As a result, several toxin chimeras have been developed that target different sensory receptors at different levels [21]. These genetically engineered neurotoxins have already shown efficacy in different animal

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_20

models of pain (see below). These animal investigations have paved the way for human studies which are currently being designed to test the clinical efficacy of these compounds in human pain disorders.

Botulinum Neurotoxin Chimeras and Their Role in Pain Management

The molecular structure of botulinum neurotoxins contains three functionally distinct domains: binding, translocating, and catalytic (Fig. 20.1). As discussed in Chap. 2, the first two domains are included in the heavy chain (HC,100 KD) of the toxin, whereas the light chain (LC, 50 KD) catalyzes and inactivates the SNARE proteins at synapse preventing the release of neurotransmitters from the presynaptic

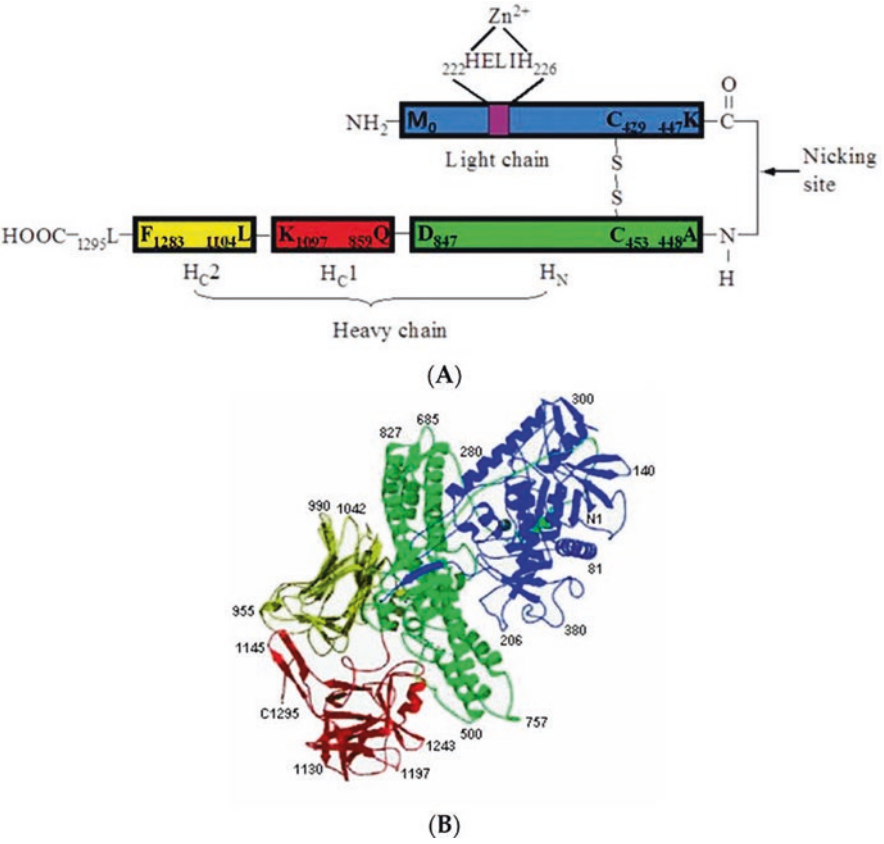

Fig. 20.1 Structure of botulinum toxin A. Light (L) and heavy (H) chains are connected by a disulfide bond. (Reproduced under creative commons attribution. From Cai et al. Micro-organisms, 2021 [22]. Courtesy of PMC publisher)

vesicles. The HC is a 100 KD protein and has two terminals, N and C. Through its C terminal, the heavy chain binds to the synaptic membrane receptors (ganglioside, SV2 in case of BoNT-A). Following binding, HC moves the toxin molecule through the synaptic membrane to the cell's interior. The light chain is a zinc-endopeptidase protein which is bound to the HC by a disulfide bond. Once inside, the light chain is detached from the HC and acts upon the synaptic proteins (SNARE) to block their function (vesicular membrane fusion and transmitter release). The function of various domains of the toxin varies between different BoNT serotypes. For instance, the binding domain of one toxin may show strong affinity for one cell receptor and weak affinity for another. BoNTs A and E cleave SNARE protein SNAP25, BoNT-C cleaves SNAP25 and Syntaxin, and BoNT-B, BoNT-D, BoNT-F, and BoNT-G cleave vesicle-associated membrane proteins (VAMP, 1,2,3). The protease of newly discovered BoNT-X is unique as it cleaves VAMP1, 2, 3, 4, and 5 and Ykt6.

Botulinum neurotoxin chimeras are genetically engineered molecules with combined domains from different toxins in order to improve the overall function of the toxins. Usually, a chimera is stronger than either of the two parent toxins. In recent years, the use of such chimeras in animal models has been able to induce less or more paralytic toxin effect, longer duration of toxins' action, or more specifically target certain cells (neuron or non-neuron). Pertaining to pain treatment, there are toxin chimeras which target specifically the sensory neurons.

The A/E chimera is an example of engineered toxin with antinociceptive activity. The efficacy of BoNT-A in treatment of chronic migraine has been attributed, at least in part, to inhibition of the release of calcitonin gene-related peptide (CGRP), a potent pro-inflammatory pain mediator [23]. Release of CGRP has been also implicated in the burning pain resulting from exposure to capsaicin (the chemical contained in hot pepper). Capsaicin exerts its effect by activating the transient receptor potential vanilloid receptor type 1 (TRPV1), expressed abundantly on the surface of sensory neurons of dorsal root ganglia (DRG) [24]. Activation of TRPV1 is essential for exocytosis of CGRP and requires an intact SNAP 25 function. However, neither BoNT-A nor BoNT-E by itself can alleviate or prevent the neuropathic pain caused by exposure to this agent. BoNT-E is more potent than A and acts faster than A on SNAP 25, but it has a shorter duration of action. It has been postulated that failure of BoNT-E in alleviating capsaicin-induced pain may be related to the paucity of specific binding receptors for this toxin on the surface of sensory cells. It has been hypothesized that an A/E toxin chimera may be effective against capsaicin-induced neuropathic pain using the powerful binding action of the type A toxin. A BoNT-A/E chimera has been engineered in which the HC domain of BoNT-A binds the toxin to sensory neuron's surface and by making a channel in the cell membrane translocates the E-protease into the synapse. This chimera effectively blocks the release of CGRP from TRP1 receptors in response to capsaicin exposure in cell cultures of sensory neurons [25]. Additional studies have shown that A/E chimera also prevents emergence of capsaicin-induced pain in animals as judged by alleviation of the behavioral manifestations of pain after peripheral exposure [4, 26].

Table 20.1 BoNTs engineering applications

BoNT	Modification	Application	Reference (s)
BoNT	Re-engineering of target specificity	Chronic pain	[27]
BoTIMs	Full length BONT incorporation—Inactive LC/A and LC/E	Prolonged effect in various pain states including chronic pain	[28–30]
BoNT/Bmy	Mutations enhancing binding to human synaptotagmin II, mutations of lipid binding loop	Enhanced efficacy	[31–34]
LC/B	Mutations of substrate recognition pocket	Novel therapy to escape immunoresistance in BoNT/B therapy	[35]
BoNT/LC	LC mutations	Maintains cleavage of syntaxin	[36, 37]
BoNT/B, triple mutant	Mutations producing protonation of residues involved in translocation process	Increased neurotoxicity due to faster neurotoxin cytosolic delivery of enzymatic domain	[38]
BoNT-A	Protein stapling allowing BoNT/A re-assembly in situ	Development of neuronal modulation agents	[39]
BoNT-A and E chimera	Chimera construction	Targeting specific population of neurons or secretory cells	[40]
BoNT/LC	Vector expressed transgenic BoNT/LC	Stable, selective and controllable, BoNT/LC in different neuronal types	[5]
BoNTS	Ligation to agents targeting BoNT delivery to specific cell types	Pain relief, reduction of inflammation and neuropathic pain	[41]

Form Rosetti-Scargueil and Propoff (slightly modified)—Toxins 2021—Courtesy of publisher. Reproduced under Creative Commons Attribution License

Rosetti-Escargueil and Propoff reviewed the literature on recently genetically engineered toxins and have provided a list of important contributions in this area (Table 20.1) [4].

Ferrari et al. [21] assembled a chimera of BoNT-A and tetanus toxin using a new technology of "protein stapling." Through this method, the C domain protease of BoNT-A was combined with the binding domain of the tetanus toxin. Tetanus toxin naturally attaches itself to central neurons. The flaccid or spastic paralysis, characteristic of exposure to BoNT-A, and tetanus toxin were not observed in the rats injected intrathecally with the chimera. Measurements of the paralytic effect of the chimera have shown that it is negligible and 11,000 times less than either parent toxin. The rats were then injected with Freund's adjuvant in the hind paw to cause local inflammation, inflammatory pain, and mechanical hypersensitivity. The animals pretreated with the novel chimera demonstrated significantly less mechanical hypersensitivity compared to the control animals that had been pretreated with saline. Cleavage of SNAP 25 was noted in approximately half of the sensory dorsal

root ganglia neurons, indicating resistance of a population of sensory neurons to this chimera. The investigators concluded that pain-conducting mechanoreceptors in the rat are located in tetanus toxin binding neurons and the novel chimera of BoNT-A/tetanus toxin has a potential for treating pain in human subjects.

Using the protein stapling technique, Andreou et al. [42] recently engineered a new botulinum toxin named BiTox-AA in which the binding parts of BoNT-A are doubled. This toxin with heavier molecular weight than the original BoNT-A toxin has 100 times less paralyzing effect than the native BoNT-A when injected into the gastrocnemius muscle. This property of Bitox-AA makes it suitable for use in pain disorders where pain originates from spasm of large muscles. Currently, use of large doses of native BoNT-A in such conditions is limited due to its paralyzing effect. Furthermore, the authors have shown that Bitox-AA specifically targets the sensory neurons. In animal models of trigeminal pain, BiTox-AA demonstrated significant efficacy in blocking activation of the trigeminal system and reducing trigeminal hyperalgesia, hence making it suitable for treatment of human migraine.

Botulinum Toxin as a Protein Transporter

The capacity of botulinum neurotoxin molecule to move a 50KD protein (light chain-LC) through synaptic membrane has inspired attempts to use BoNTs as vehicles to carry small size proteins into cells for therapeutic purposes. A variety of approaches has been used in recent years including gene transfer into neuroblastoma cells and transport of viral vectors into neural cells [43]. Ma et al. [44] engineered a recombinant small molecule antibody, scFv, which works against the P2X3 nociceptive receptor; P2X3 is believed to play a major role in the development of inflammatory pain [45]. Drugs that reduce the action of this purinergic ATP-activated receptor have been shown to alleviate neuropathic inflammatory pain [46]. A fused protein was generated by ligating the gene of scFv antibody to the gene of BoNT-A [44]. This compound enters the sensory neurons that have P2X3 receptors and cleaves the SNAP 25. The cleavage of SNAP 25 with this novel protein occurs in much lower concentration (at 0.1 nm level) compared to BoNT alone (at 100 nm). The novel protein also inhibited the release of CGRP from the sensory neurons (DRG).

More Recent Innovations

Blum et al. [47], through phage-assisted technology, were able to retarget the proteases of BoNT-X and BoNT-E, opening a new area of retargeting BoNT proteases that can have distinct utility in many areas of medicine. The technique couples the desired properties of certain protease domains to the infectivity of a bacteriophage (virus that replicates inside bacteria) and allows it to rapidly evolve over many

generations. It offers a significant potential for treatment of chronic pain, as protease domains of BoNTs may specifically cleave proteins that are involved in pain sensation [48].

Wang et al. [49] identified a promoter for Pirt (phosphoinositide interacting regulator of TRP) and cloned it into a lentiviral vector that was able to drive trans-gene selectivity into peripheral sensory neurons. Pirt is naturally expressed in peripheral sensory neurons. This viral mediated expression of the rapidly cleaved SNAP 25 in the sensory neurons, downregulated expression of pain-related genes in cultures of sensory neurons; these genes are usually stimulated by pro-inflammatory cytokines. The downregulated genes include calcitonin gene-relater peptide 2, TRP1, and sodium voltage-gated channel subunit 9, among others. The authors emphasized the potential of this technique for treatment of pain disorders.

A new BoNT named CCUG 7968 (INI101) has been developed recently [50]. This toxin, although unlike other BoNTs, is not a Hall A toxin strain and acts the same as currently utilized neurotoxins after intramuscular injection. This new toxin blocks release of acetylcholine from neuromuscular junction and causes reversible muscular atrophy. It produces no toxicity in rats with the applied dose of 2–8 units. Compared to currently used BoNTs, INI101 shows less perfusion into the surrounding tissue. This toxin's effect on sensory neurons and pain needs to be explored.

Allen et al. [51] recently engineered a BoNT chimera (C2C) that selectively targeted the sensory neurons and after intramuscular injection relieved inflammatory pain in rats. This C1-C2 hybrid causes actin remodeling through protein ribosylation of G-Actin. Mice injected subcutaneously by C2C demonstrated colonization of C2C with CGRP positive neurons and fibers, but not with motor neurons and fibers. Furthermore, subcutaneous injection C2C toxin in mice suffering from pain related to formalin injection, similar to opioids, reduced pain in 90% of the tested animals.

The newly engineered BoNT-Bs [52] can also have the potential to treat human pain. Native BoNT-B after intramuscular injection reduces the effect of substance P in DRG and spinal neurons [3]. The engineered BoNT-Bs (rBonT-Bmy) and (rBoNT-Bqw) show enhanced affinity for attachment to known cell surface receptor of the BoNT-B toxin, namely, synaptotagmin 2 (hSyt2). It is believed that this property enhances the action of the engineered B toxin and makes it more effective than the native toxin.

Comment

Recent advances in genetic engineering have led to development of several BoNT chimeras with a potential for targeting peripheral and spinal sensory neurons. Furthermore, the newly engineered BoNTs have more efficacy and less toxicity. The recently developed, novel phage-assisted technique that uses viral bacteriophage has a great potential to deliver different proteases (including that of botulinum toxins) to different cells among them the sensory neurons. These scientific advances

will hopefully improve the prospect of BoNT therapy in human chronic pain disorders.

References

1. Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int. 2008;101:366–70.
2. Marinelli S, Luvisetto S, Cobianchi S, Makuch W, Obara I, Mezzaroma E, Caruso. Botulinum neurotoxin type A counteracts neuropathic pain and facilitates functional recovery after peripheral nerve injury in animal models. Neuroscience. 2010;171:316–28.
3. Marino MJ, Terashima T, Steinauer JJ, Eddinger KA, Yaksh TL, Xu Q. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155:674–84.
4. Meng J, Wang J, Lawrence G, Dolly JO. Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. J Cell Sci. 2007;120:2864–74.
5. Joussain C, Le Coz O, Pichugin A, Marconi P, Lim F, Sicurella M, Salonia A, Montorsi F, Wandosell F, Foster K, Giuliano F, Epstein AL, Aranda MA. Botulinum neurotoxin light chains expressed by defective herpes simplex virus type-1 vectors cleave SNARE proteins and inhibit CGRP release in rat sensory neurons. Toxins (Basel). 2019;11(2):123. https://doi.org/10.3390/toxins11020123.
6. Rapp DE, Turk KW, Bales GT, Cook SP. Botulinum toxin type a inhibits calcitonin gene-related peptide release from isolated rat bladder. J Urol. 2006;175(3 Pt 1):1138–42. https://doi.org/10.1016/S0022-5347(05)00322-8.
7. Melo-Carrillo A, Strassman AM, Schain AJ, Noseda R, Ashina S, Adams A, Brin MF, Burstein R. Exploring the effects of extracranial injections of botulinum toxin type A on prolonged intracranial meningeal nociceptors responses to cortical spreading depression in female rats. Cephalalgia. 2019;39(11):1358–65. https://doi.org/10.1177/0333102419873675.
8. Matak I, Tékus V, Bölcskei K, Lacković Z, Helyes Z. Involvement of substance P in the anti-nociceptive effect of botulinum toxin type A: evidence from knockout mice. Neuroscience. 2017;358:137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040.
9. Bossowska A, Lepiarczyk E, Mazur U, Janikiewicz P, Markiewicz W. Botulinum toxin type A induces changes in the chemical coding of substance P-immunoreactive dorsal root ganglia sensory neurons supplying the porcine urinary bladder. Toxins (Basel). 2015;7(11):4797–816. https://doi.org/10.3390/toxins7114797.
10. Sikandar S, Gustavsson Y, Marino MJ, Dickenson AH, Yaksh TL, Sorkin LS, Ramachandran R. Effects of intraplantar botulinum toxin-B on carrageenan-induced changes in nociception and spinal phosphorylation of GluA1 and Akt. Eur J Neurosci. 2016;44(1):1714–22. https://doi.org/10.1111/ejn.13261.
11. da Silva LB, Poulsen JN, Arendt-Nielsen L, Gazerani P. Botulinum neurotoxin type A modulates vesicular release of glutamate from satellite glial cells. J Cell Mol Med. 2015;19(8):1900–9. https://doi.org/10.1111/jcmm.12562.
12. Bittencourt da Silva L, Karshenas A, Bach FW, Rasmussen S, Arendt-Nielsen L, Gazerani P. Blockade of glutamate release by botulinum neurotoxin type A in humans: a dermal microdialysis study. Pain Res Manag. 2014;19(3):126–32. https://doi.org/10.1155/2014/410415.
13. Hong B, Yao L, Ni L, Wang L, Hu X. Antinociceptive effect of botulinum toxin A involves alterations in AMPA receptor expression and glutamate release in spinal dorsal horn neurons. Neuroscience. 2017;357:197–207. https://doi.org/10.1016/j.neuroscience.2017.06.004.

14. Yang KY, Mun JH, Park KD, Kim MJ, Ju JS, Kim ST, Bae YC, Ahn DK. Blockade of spinal glutamate recycling produces paradoxical antinociception in rats with orofacial inflammatory pain. Prog Neuro-Psychopharmacol Biol Psychiatry. 2015;57:100–9. https://doi.org/10.1016/j.pnpbp.2014.10.011.
15. Wang J, Xu W, Kong Y, Huang J, Ding Z, Deng M, Guo Q, Zou W. SNAP-25 contributes to neuropathic pain by regulation of VGLuT2 expression in rats. Neuroscience. 2019;423:86–97. https://doi.org/10.1016/j.neuroscience.2019.10.007. Erratum in: Neuroscience. 2020; 437:256
16. Blasi J, 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. https://doi.org/10.1038/365160a0.
17. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012;61:236–9.
18. Antonucci F, Rossi C, Gianfranceschi L, Rossetto O, Caleo M. Long-distance retrograde effects of botulinum neurotoxin A. J Neurosci. 2008;28:3689–96. https://doi.org/10.1523/JNEUROSCI.0375-08.2008.
19. Restani L, Antonucci F, Gianfranceschi L, Rossi C, Rossetto O, Caleo M. Evidence for anterograde transport and transcytosis of botulinum neurotoxin A (BoNT/A). J Neurosci. 2011;31:15650–9. https://doi.org/10.1523/JNEUROSCI.2618-11.2011.
20. Restani L, Novelli E, Bottari D, Leone P, Barone I, Galli-Resta L, Strettori E, Caleo M. Botulinum neurotoxin A impairs neurotransmission following retrograde transynaptic transport. Traffic. 2012;13:1083–9. https://doi.org/10.1111/j.1600-0854.2012.01369.x.
21. Ferrari E, Gu C, Niranjan D, Restani L, Rasetti-Escargueil C, Obara I, Geranton SM, Arsenault J, Goetze TA, Harper CB, Nguyen TH, Maywood E, O'Brien J, Schiavo G, Wheeler DW, Meunier FA, Hastings M, Edwardson JM, Sesardic D, Caleo M, Hunt SP, Davletov B. Synthetic self-assembling clostridial chimera for modulation of sensory functions. Bioconjug Chem. 2013;24:1750–9.
22. Cai S, Kumar R, Singh BR. Clostridial neurotoxins: structure, function and implications to other bacterial toxins. Microorganisms. 2021;9(11):2206. https://doi.org/10.3390/microorganisms9112206.
23. Cernuda-Morollón E, Martínez-Camblor P, Ramón C, Larrosa D, Serrano-Pertierra E, Pascual J. CGRP and VIP levels as predictors of efficacy of onabotulinumtoxin type A in chronic migraine. Headache. 2014;54:987–95.
24. Nagy I, Friston D, Valente JS, Torres Perez JV, Andreou AP. Pharmacology of the capsaicin receptor, transient receptor potential vanilloid type-1 ion channel. Prog Drug Res. 2014;68:39–76.
25. Meng J, Ovsepian SV, Wang J, Pickering M, Sasse A, Aoki KR, Lawrence GW, Dolly JO. Activation of TRPV1 mediates calcitonin gene-related peptide release, which excites trigeminal sensory neurons and is attenuated by a retargeted botulinum toxin with antinociceptive potential. J Neurosci. 2009;29:4981–92.
26. Rasetti-Escargueil C, Popoff MR. Engineering botulinum neurotoxins for enhanced therapeutic applications and vaccine development. Toxins (Basel). 2020;13(1):1. https://doi.org/10.3390/toxins13010001.
27. Foster KA, Bigalke H, Aoki KR. Botulinum neurotoxin–from laboratory to bedside. Neurotox Res. 2006;9:133–40. https://doi.org/10.1007/BF03033931.
28. Wang J, Zurawski TH, Bodeker MO, Meng J, Boddul S, Aoki KR, Dolly JO. Longer-acting and highly potent chimaeric inhibitors of excessive exocytosis created with domains from botulinum neurotoxin A and B. Biochem J. 2012;444:59–67.
29. Dolly JO, Lawrence GW, Meng J, Wang J, Ovsepian SV. Neuro-exocytosis: botulinum toxins as inhibitory probes and versatile therapeutics. Curr Opin Pharmacol. 2009;9:326–35. https://doi.org/10.1016/j.coph.2009.03.004.
30. Wang L, Wang K, Chu X, Li T, Shen N, Fan C, Niu Z, Zhang X, Hu L. Intra-articular injection of botulinum toxin A reduces neurogenic inflammation in CFA-induced arthritic rat model. Toxicon. 2017;126:70–8. https://doi.org/10.1016/j.toxicon.2016.11.009.

31. Tao L, Peng L, Berntsson RP, Liu SM, Park S, Yu F, Boone C, Palan S, Beard M, Chabrier PE, et al. Engineered botulinum neurotoxin B with improved efficacy for targeting human receptors. Nat Commun. 2017;8:53. https://doi.org/10.1038/s41467-017-00064.
32. Elliott M, Favre-Guilmard C, Liu SM, Maignel J, Masuyer G, Beard M, Boone C, Carre D, Kalinichev M, Lezmi S, et al. Engineered botulinum neurotoxin B with improved binding to human receptors has enhanced efficacy in preclinical models.
33. Yin L, Masuyer G, Zhang S, Zhang J, Miyashita SI, Burgin D, Lovelock L, Coker SF, Fu TM, Stenmark P, et al. Characterization of a membrane binding loop leads to engineering botulinum neurotoxin B with improved therapeutic efficacy. PLoS Biol. 2020;18:e3000618.
34. Fonfria E, Elliott M, Beard M, Chaddock JA, Krupp J. Engineering botulinum toxins to improve and expand targeting and SNARE cleavage activity. Toxins. 2018;10:278. https://doi.org/10.3390/toxins10070278.
35. Guo J, Pan X, Zhao Y, Chen S. Engineering clostridia neurotoxins with elevated catalytic activity. Toxicon. 2013;74:158–66. https://doi.org/10.1016/j.toxicon.2013.08.055.
36. Zanetti G, Sikorra S, Rummel A, Krez N, Duregotti E, Negro S, Henke T, Rossetto O, Binz T, Pirazzini M. Botulinum neurotoxin C mutants reveal different effects of syntaxin or SNAP-25 proteolysis on neuromuscular transmission. PLoS Pathog. 2017;13:e1006567. https://doi.org/10.1371/journal.ppat.1006567.
37. Wang J, Zurawski TH, Meng J, Lawrence G, Olango WM, Finn DP, Wheeler L, Dolly JO. A dileucine in the protease of botulinum toxin A underlies its long-lived neuroparalysis: transfer of longevity to a novel potential therapeutic. J Biol Chem. 2011;286:6375–85. https://doi.org/10.1074/jbc.M110.181784.
38. Pirazzini M, Henke T, Rossetto O, Mahrhold S, Krez N, Rummel A, Montecucco C, Binz T. Neutralisation of specific surface carboxylates speeds up translocation of botulinum neurotoxin type B enzymatic domain. FEBS Lett. 2013;587:3831–6. https://doi.org/10.1016/j.febslet.2013.10.010.
39. Ferrari E, Maywood ES, Restani L, Caleo M, Pirazzini M, Rossetto O, Hastings MH, Niranjan D, Schiavo G, Davletov B. Re-assembled botulinum neurotoxin inhibits CNS functions without systemic toxicity. Toxins. 2011;3:345–55. https://doi.org/10.3390/toxins3040345.
40. Wang J, Meng J, Lawrence GW, Zurawski TH, Sasse A, Bodeker MO, Gilmore MA, Fernandez-Salas E, Francis J, Steward LE, et al. Novel chimeras of botulinum neurotoxins A and E unveil contributions from the binding, translocation, and protease domains to their functional characteristics. J Biol Chem. 2008;283:16993–7002.
41. Tang M, Meng J, Wang J. New engineered-botulinum toxins inhibit the release of pain-related mediators. Int J Mol Sci. 2019;21:262. https://doi.org/10.3390/ijms21010262.
42. Andreou AP, Leese C, Greco R, Demartini C, Corrie E, Simsek D, Zanaboni A, Koroleva K, Lloyd JO, Lambru G, Doran C, Gafurov O, Seward E, Giniatullin R, Tassorelli C, Davletov B. Double-binding botulinum molecule with reduced muscle paralysis: evaluation in in vitro and in vivo models of migraine. Neurotherapeutics. 2021;18(1):556–68. https://doi.org/10.1007/s13311-020-00967-7.
43. Masuyer G, Chaddock JA, Foster KA, Acharya KR. Engineered botulinum neurotoxins as new therapeutics. Annu Rev Pharmacol Toxicol. 2014;54:27–51.
44. Ma H, Meng J, Wang J, Hearty S, Dolly JO, O'Kennedy R. Targeted delivery of a SNARE protease to sensory neurons using a single chain antibody (scFv) against the extracellular domain of P2X3 inhibits the release of a pain mediator. Biochem J. 2014;462:247–56.
45. Burnstock G. Physiopathological roles of p2x receptors in the central nervous system. Curr Med Chem. 2014.
46. Dai Y, Fukuoka T, Wang H, Yamanaka H, Obata K, Tokunaga A, Noguchi K. Contribution of sensitized P2X receptors in inflamed tissue to the mechanical hypersensitivity revealed by phosphorylated ERK in DRG neurons. Pain. 2004;108:258–66.
47. Blum TR, Liu H, Packer MS, Xiong X, Lee PG, Zhang S, Richter M, Minasov G, Satchell KJF, Dong M, Liu DR. Phage-assisted evolution of botulinum neurotoxin proteases with

reprogrammed specificity. Science. 2021;371(6531):803–10. https://doi.org/10.1126/science.abf5972.
48. Stenmark P. Re-engineering Botox. Science. 2021;371(6531):782. https://doi.org/10.1126/science.abg3535.
49. Wang W, Kong M, Dou Y, Xue S, Liu Y, Zhang Y, Chen W, Li Y, Dai X, Meng J, Wang J. Selective expression of a SNARE-cleaving protease in peripheral sensory neurons attenuates pain-related gene transcription and neuropeptide release. Int J Mol Sci. 2021;22(16):8826. https://doi.org/10.3390/ijms22168826.
50. An Y, Kim YJ, Kim CS, Yim H, Kim M, Lee EK, Oh HJ, Han JH, Yoo E, Kim S, Woo J, Moore ERB, Jung JY, Park W. Therapeutic efficacy of new botulinum toxin identified in CCUG 7968 strain. Appl Microbiol Biotechnol. 2021;105(23):8727–37. https://doi.org/10.1007/s00253-021-11640-0.
51. Allen D, Zhou Y, Wilhelm A, Blum P. Intracellular G-actin targeting of peripheral sensory neurons by the multifunctional engineered protein C2C confers relief from inflammatory pain. Sci Rep. 2020;10(1):12789. https://doi.org/10.1038/s41598-020-69612-9.
52. Elliott M, Favre-Guilmard C, Liu SM, Maignel J, Masuyer G, Beard M, Boone C, Carré D, Kalinichev M, Lezmi S, Mir I, Nicoleau C, Palan S, Perier C, Raban E, Zhang S, Dong M, Stenmark P, Krupp J. Engineered botulinum neurotoxin B with improved binding to human receptors has enhanced efficacy in preclinical models. Sci Adv. 2019;5(1):eaau7196. https://doi.org/10.1126/sciadv.aau7196.

Correction to: Botulinum Toxin in Dentistry and Treatment of Chronic Orofacial Pain

Shahroo Etemad-Moghadam, Mojgan Alaeddini, and Bahman Jabbari

Correction to:
Chapter 16 in: *B. Jabbari, Botulinum Toxin Treatment of Pain Disorders*, https://doi.org/10.1007/978-3-030-99650-5_16

This chapter was incorrectly published with a mistake in Chapter 16. The names of three co-authors which should have been added to the chapter were left out.

The authors' names should read:

Shahroo Etemad-Moghadam, Mojgan Alaeddini, Bahman Jabbari.
The book has also been updated to reflect this change.

The updated version of this chaparter can be found at
https://doi.org/10.1007/978-3-030-99650-5_16

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5_21

Index

B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
https://doi.org/10.1007/978-3-030-99650-5