Chapter 5
Pain Disorders other than Migraine

Abstract Following injection into the muscle or skin, botulinum toxin blocks the release of pain transmitters and modulators and lead to reduction of pain perception. Botulinum toxin treatment (with Botox) is now approved by FDA for treatment of chronic migraine (Chap. 4). High quality studies have shown efficacy of botulinum toxins in several pain syndromes including local pain in diabetic neuropathy, pain after shingles (post-herpetic neuralgia), pain after trauma to the limb, face pain in trigeminal neuralgia, heal pain in plantar fasciitis, non-surgical low back pain, pain associated with Raynaud syndrome and deep buttock pain in piriformis syndrome. Preliminary studies in several other pain syndrome have also demonstrated encouraging results. At the present time, none of these potential pain indications are FDA approved.

Keywords Botulinum toxin · Botulinum neurotoxin · Pain · Diabetic neuropathy · Neuralgia · Low back pain · Plantar faciitis · Raynaud syndrome

Introduction

Pain is the most common human medical complaint. International Association for the Study of Pain (IASP) defines chronic pain as a pain that persists 3 months or longer [1]. The prevalence of chronic pain in US is reported as 20% [2] comparable with that of Europe (19%) [3], where the highest prevalence for pain (30%) is reported for Poland [3]. Patient with chronic pain suffer from impaired quality of life [4]. In US, a report published in 2011, estimated the cost of chronic pain management (including direct health care cost and lost productivity) ranging from 560 to 635 billion dollars annually [5].

In most patients, pain is generated from a noxious stimulus which irritates the skin and peripheral nerves (peripheral pain). Central pain is uncommon. Less than 10% of pain experienced by the general population, is generated from a disease or disorder of the central nervous system (spinal cord or brain). This central pain can be seen is conditions such as stroke, multiple sclerosis or trauma to the brain or spinal cord.

B. Jabbari, *Botulinum Toxin Treatment*,
https://doi.org/10.1007/978-3-031-54471-2_5

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

Anatomy of Pain Pathways

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

Transduction

In this first phase of pain pathway, a noxious peripheral stimulus (thermal, mechanical, chemical) stimulates the peripheral sensory nerve endings which are scattered in the skin, muscle and joints. Located on these sensory nerve endings, are small receptors capable of sensing various types of the peripheral stimulation (heat, pressure, chemical). These receptors which are called nociceptive (related to pain) receptors are also present on the body of the central sensory nerve cells (neurons) in the spinal cord. The pain which arises from damage to the tissue (skin, muscle, joint) is called nociceptive pain, whereas the term neuropathic pain is applied to pain arising from damage to a peripheral nerve or the sensory pathways in the central nervous system.

Noxious stimulation of sensory nerve endings causes local secretion of several chemicals from the nerve endings which elicit stimulation of specific pain receptors. Furthermore, local tissue inflammation caused by accumulation of these chemicals leads to more stimulation of the nerve endings resulting in peripheral sensitization. Some of these chemicals such as histamine, bradykinin, Substance P and calcitonin gene-related peptide (CGRP) are well known; several others are currently under investigation.

Transmission

During this phase, electrical activity that is generated from stimulation of the above-mentioned receptors travels along the sensory nerve. Sensory nerve fibers have different sizes. The fibers that convey the pain modality are thin (A-delta fiber) or very

thin (C fibers). A-delta fibers conduct faster and are responsible for the short lasting and very sharp initial pain felt after exposure to a noxious stimulus. Slow conducting, C fibers produce the less intense, but longer lasting pain that follows the initial sharp pain (Fig. 5.1, lower right).

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

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

Pain Modulation

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

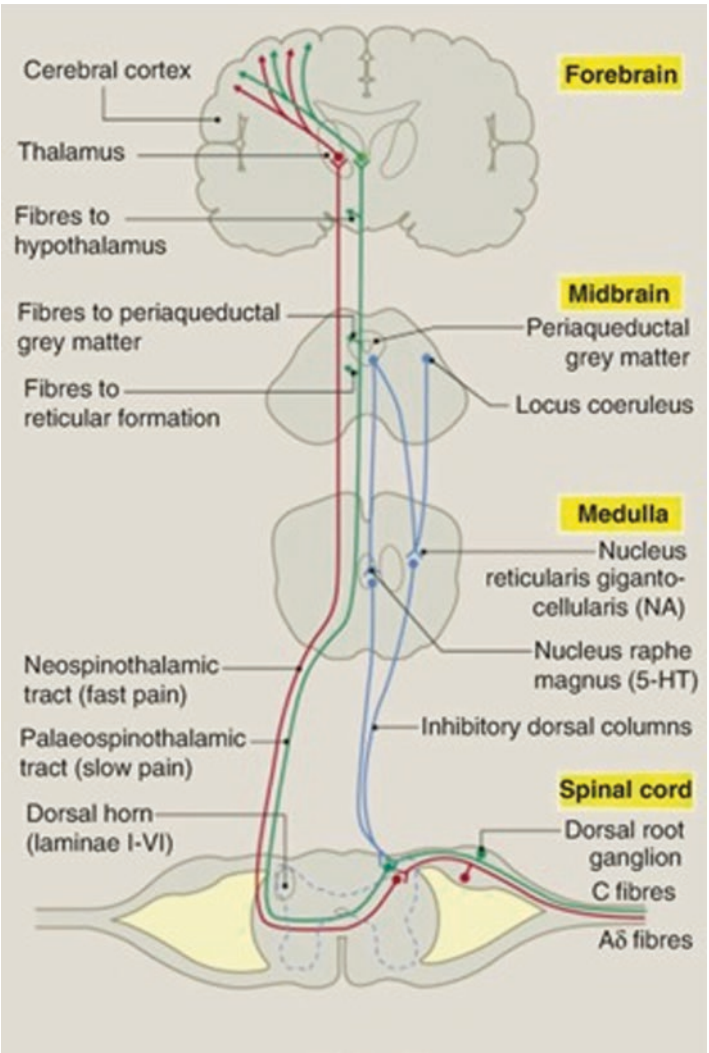

Fig. 5.1 Pain pathways. (From Steeds Anatomy and Physiology of Pain, Surgery (Oxford) 2016—Reprinted with permission from Elsevier)

Pain Perception

The pain signals which reach the thalamus from the periphery reach three areas of the cerebral cortex (a layer of cells that cover the brain) (Fig. 5.2): the somatosensory cortex which is located in the parietal lobe and localizes the physical sensations including pain, the limbic system consisting of a group of cells located in the medial aspect of the temporal and the frontal lobes dealing with the emotional aspect of

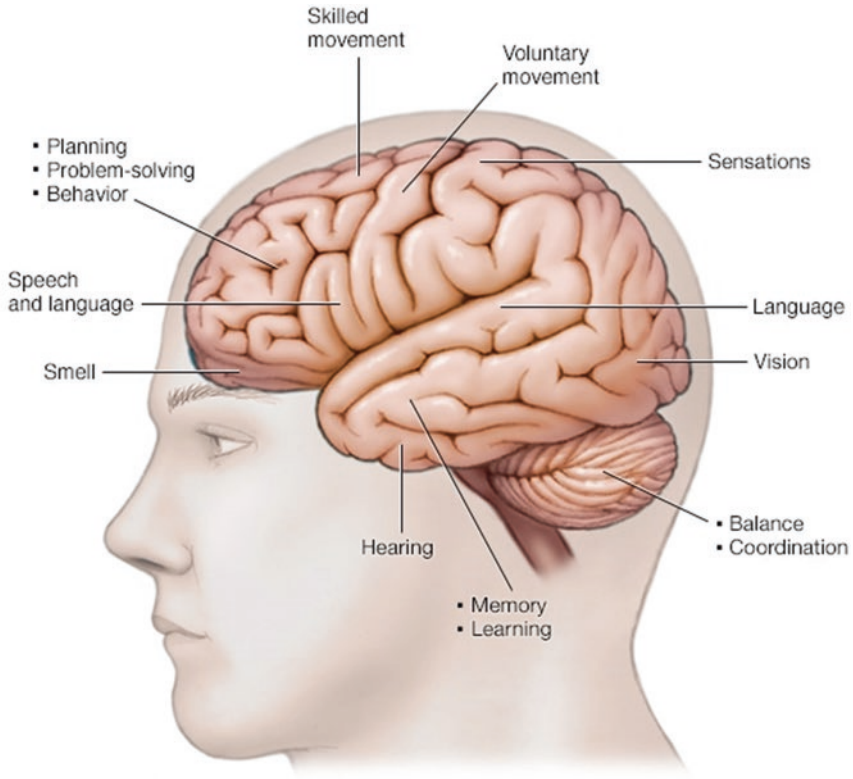

Fig. 5.2 Four lobes of the brain representing different functions. The lobe located in front of the head is the frontal lobe. Posterior to that is parietal lobe that deals with sensations including pain. The temporal lobe in in the temple region deals with memory and hearing among other functions

painful stimuli and the frontal cortex that processes meaning and cognition of nociception (pain). The perception of pain therefore, involves multiple cortical structures which combine sensation, emotion and conscious thought.

A Brief Review of Animal Studies of Botulinum Toxins in the Field of Pain

Over the past 30 years, a large number of animal studies have shown that injection of botulinum toxins to animals can inhibit secretion of pain transmitters and prevent or reduce the pain behavior. Although most of these studies have been performed with onabotulinumtoxinA (Botox), studies with other type A toxins and with the

type B toxin are also forthcoming (see Chaps. 2 and 3 for definition of different botulinum toxins). These studies have demonstrated that botulinum toxins can affect pain transmission via their influence upon nerve endings, dorsal root ganglia (DRG) and spinal cord sensory neurons.

Nerve Endings and Peripheral Receptors

In formalin model of pain, injection of formalin into the rat's paw causes severe sharp pain which lasts for seconds and then a less severe pain that last longer, minutes to hours. The first peak of this pain is due to the acute irritation of nerve endings by formalin, whereas the second pain represents the irritating effect of local inflammation caused by formalin injection. Examination of the injected tissue (rat's paw) shows local accumulation of glutamate, a known pain transmitter and local presence of inflammatory cells. Injection of botulinum toxin type A (Botox) and type B toxin (Myobloc), 5 days before formalin injection, markedly reduces the inflammatory peak of pain (second peak) and lowers accumulation of glutamate at the injected tissue [6, 7].

Dorsal Root Ganglion

When cultured, nerves cells of dorsal root ganglia (DRG), the first sensory nerve cell (neurons) (Fig. 5.1, lower right) which receive pain signals from the periphery, secrets substance P, a pain transmitter. Adding Botox to this culture inhibits the release of substance P from DRG nerve cultures [8].

Spinal Cord Sensory Neurons

It has been shown, in animals, that after intramuscular injection, the receptor protein that receives Botox at nerve-muscle junction (SNAP 25, see Chap. 1 for more detailed description) travels to the spinal cord and influences the spinal sensory nerve cells (second sensory neurons which receive pain signals) [9]. Furthermore, injection of botulinum toxin B into the paw of the rat reduces release of substance P (a chemical pain transmitter) from the spinal neurons after formalin activation [7].

Several other studies, both in animals and in human, have shown that injection of botulinum toxin into muscle or skin can diminish induced pain sensation by influencing the pain transmitters at or above the spinal cord level [7, 10–15].

Human Pain Syndromes

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

Chronic Low Back Pain

Low back pain is defined as a pain that occurs between 12th rib (last and the lowest rib) and the end of the lumbar spine at the region of iliac crest. Epidemiological studies have demonstrated that 75–80% of all people suffer from low back pain sometime during their lifetime [16]. Chronic low back pain is defined as a low back pain that lasts more than 6 months. Between 2% and 7% of patients with acute low back pain develop chronic low back pain. Low back pain is a major burden to the US and European economy with a disability rate of 11–12% [17].

Low back pain has different causes and can arise from ailment of different structures in the low back area. Lumbar spine consists of five bones (vertebrae) each separated by a soft disc and wrapped by several layers of muscles and tendons which maintain its stability. The spinal cord which is located inside the spinal column ends just above the lumbar spine but nerve fibers that supply motor and sensory function of the legs emerge from the end of the spinal cord and travel to the legs after passing between the five lumbar vertebrae. These nerve roots after leaving lumbar column (vertebrae) join together and constitute the major nerve supply of the leg. For instance, sciatic nerve is made from nerve roots that come from fourth and fifth lumbar roots joining with the first three sacral roots (sacrum is part of the pelvis).

Structural damage to the lumbar bones (trauma, tumor, infection) or herniated discs can apply pressure to the nerve roots and cause low back pain. Congenital spinal stenosis (narrowing) can also cause low back pain at some point in life. Low back pain can also arise from tightness of the muscles that surround the lumbar column. Sometimes these muscles on examination, demonstrate areas sensitive to pressure which are termed trigger points (pressure upon them triggers pain). Unfortunately, in most patients with chronic low back pain radiological procedures such as CT scan or MRI do not disclose significant lesions (herniated disc or other abnormalities) amenable to surgical remedy. Non-specific findings such as bone degeneration are often found in the elderly's individual examinations.

Management of chronic low back pain is a major medical challenge. A recent review of this subject details pharmacological and non-pharmacological approaches for treatment of low back pain [18]. Non-pharmacological approaches include behavioural management, special exercises, massage, superficial heat, acupuncture, yoga, Tai chi, operant (psychological) therapy and chiropractic manipulation.

Pharmacological therapy starts with non-steroidal, anti-inflammatory drugs (aspirin, tylenol, others). The American College of Physicians' guidelines recommend duloxetine and tramadol as secondary line of treatment for chronic low back pain. When the pain is neuropathic (secondary to peripheral nerve or spinal cord damage, often with a burning quality) gabapentin is recommended. Opioids are effective, but due to their potential for addiction, should be kept as the last resort and used sparingly. Lumbar epidural steroid injection may provide temporary pain relief, but reinjections are often required. Radiofrequency sacroiliac joint stimulation and spinal cord stimulation may provide temporary relief as well. Surgery is indicated in a limited number of patients more often in patients with acute low back pain related to herniated disc. Failure after surgery is not uncommon. The term failed back syndrome is used for low back pain continuing after surgery.

Botulinum Toxin Treatment of Chronic Low Back Pain

Botulinum toxin treatment of chronic low back pain is based on the premise that intramuscular injection of botulinum toxin can relax the tense muscles by blocking the release of acetylcholine from nerve terminals at nerve-muscle junction. As described before, acetylcholine that is released from the end of peripheral nerves activates the muscle leading to muscle movement and muscle contraction. Furthermore, as described above, injection of botulinum toxin into the muscle or skin can diminish or abolish pain by reducing the function of pain transmitters and pain modulators. For these reasons, over the past 25 years, several investigators have explored the efficacy of botulinum toxin therapy in chronic low back pain. These studies were done with different toxins and under different protocols. Among different studies, two high quality studies (albeit including small number of patients), statistically produced significant improvement of chronic low back pain not amenable to surgery. This research was conducted first at the Walter Reed Army Medical Center at Washington DC and then was repeated, with the same design, at the Yale University in New haven, CT.

Walter Reed-Yale Protocol

This protocol is based on the premise that in chronic low back pain not amenable to surgery tightness of extensor back muscles (also called erector spinae-ES, Fig. 5.3) plays a pivotal role in chronicity of pain. Increased tone of these muscles can be seen in recording of these muscles electrical activity at rest by electromyography and even sometimes, by palpation during clinical examination. Extension of the spine results from the function a powerful muscle in the lumbar region called erector spinae (ES). Erector spinae is made from three long muscles that originate from the base of the neck and after traveling through the upper back join together at level of the upper lumbar region. The lower end of ES attaches to the pelvic bone (Fig. 5.3). This single bulk of the three joined muscles (ES), extends and straightens the spine. The Walter Reed-Yale protocol calls for five injections into the ES, one at

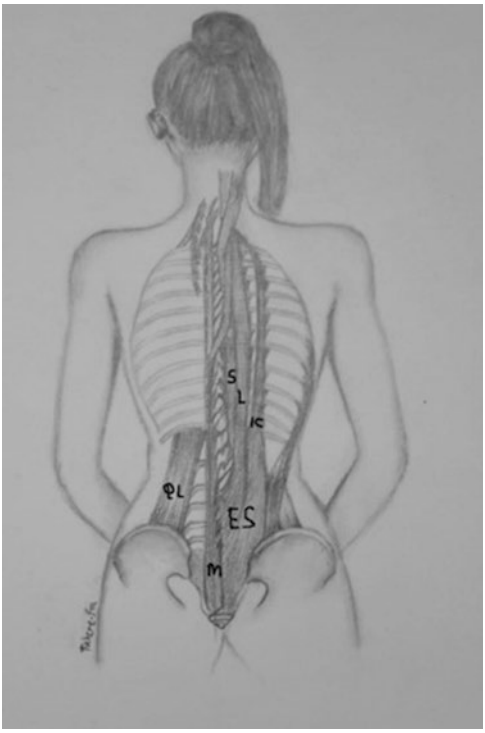

Fig. 5.3 Major muscles of low back: superficial layer (ES-shown on the right); deep layer; quadratus lumborum (QL) and multifidus (M) shown on the left. The spinalis (marked S), longisimus (marked L) and iliocostalis (IC) join at T12-L1 level to form a single mass, the erector spinae (ES) at the lumbar region. (Drawing, courtesy of Tahere Mousavi. M.D.)

each lumbar level (L1 to L5). The injections are carried under the guidance of electromyography (EMG), a technique that monitors the electrical activity of the muscle. The injections are performed with a special thin and hollow needle connected to EMG unit and the syringe that contains the botulinum toxin. Patients are instructed to extend their backs. If needle is inserted properly in the extensor muscle, the noise of the muscle activity on EMG ascertains its proper placement into the extensor muscle and the botulinum toxin is then injected through the same needle into the muscle.

Using this technique, Jabbari and co-workers have investigated the effect of botulinum toxin injection into ES muscles via two double-blind, placebo-controlled studies in patients with chronic low back pain [19, 20]. All patients had failed treatment with three or more medications for low back pain previously and had low back pain for more than 6 months. None had surgery and their CT or MRI showed no significant lesion(s) requiring surgery. The first study was conducted with Botox on 27 patients at Walter Reed Army Medical Center in Washington DC [19]. The second study was performed 10 years later at Yale University, using an identical protocol and technique on 33 patients [20]. The toxin used for the second study was Dysport, another type A toxin similar to Botox (for definition of toxin types see Chap. 3). Each unit of Botox equals approximately 2.5–3 units of Dysport. The first study was on patients with unilateral, or predominantly unilateral, low back pain. Patients received 40 units of Botox into the ES muscle at each of the 5 lumbar levels

(total of 200 units). In the second study (Yale study), some patients had unilateral, whereas others had bilateral low back pain. They received 100 units of Dysport (approximately 40 units of Botox) into ES at each lumbar level. In unilateral low back pain, the total dose of Dysport was 500 and in bilateral low back pain it was 1000 units.

The results of the two studies were almost identical. Significant pain relief was reported by 52% and 54% of the patients who received botulinum toxin, respectively. Majority of the patients in the toxin groups (but not in the placebo group) also reported improvement of their quality of life. Patients who were injected with botulinum toxin did not experience any significant side effects (weakness of the back or legs) in either of the two studies. A few patients (5%) developed a transient, mild flu like syndrome lasting a few days which is expected to happen in small percentage of patients after botulinum toxin therapy. In an open label study (not blinded), Jabbari and his colleagues treated 75 patients suffering from chronic low back pain with the same protocol over 14 months. Patients received botulinum toxin injections for low back pain every 3–4 months. Again, over 50% of patients reported significant pain relief. The positive effect of treatment was sustained over 14 months [21]. In a smaller study using Dysport and Walter Reed-Yale technique, authors reported that 76% of patients who received Dysport reported significant pain relief after 3 weeks versus 20% of those who received placebo [22]. Another study with follow up of 6 months also found injection of botulinum toxin in low back muscles was beneficial to the patients for management of low back pain with a low incidence of side effects (two patients reported mild pain at the site of injection) [23].

Other investigators who have not used Walter Reed-Yale Technique and used lower doses of Botox did not report significant improvement of low back pain [24]. Likewise injection of deeper muscles of the back (quadratus lumborum and iliopsoas—see Fig. 5.3) with Botox failed to improve low back pain [25].

Patient Observation

A 65 year-old man who had experienced low back pain for several years was referred to Yale Botulinum Toxin Clinic for evaluation. There was no history of back injury or surgical intervention. The pain affected the low back in the mid-lumbar region with no radiation to the lower limbs. A magnetic resonance imaging of the back showed diffuse degenerative spine disease but no acute pathology. Treatment with a large number of painkillers had not been helpful. The patient's examination was normal except for slightly increased muscle tone in the low back area. Since the pain was predominantly on the right side, the patient was injected on the right side only (Fig. 5.4). The injection was into the extensors of the spine (erector spinae muscle) and performed at five lumbar levels. The dose of Botox was 40 units per injection site for a total of 200 units. After a week, patient reported significant improvement of his low back pain. Over a 3 year period of follow up, he received Botox injections every 3–4 months and each time reported satisfaction with the therapy. He experienced no side effects.

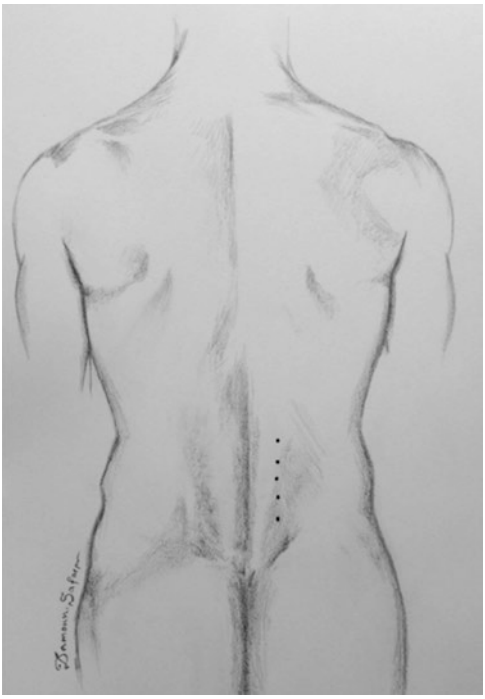

Fig. 5.4 The site of lumbar injections into ES (erector Spinae-extensor of spine). (Drawing courtesy of Dr. Damoun Safarpour)

At present, using the criteria of the Guidance Development Subcommittee of the American Academy of Neurology [26, 27] the efficacy for botulinum toxin therapy is at level B (probably effective) based on two class II studies (high quality studies with small size of cohorts). Based on these data, botulinum toxin therapy should be considered for patients with chronic low back pain who are not candidates for surgery and have repeatedly failed medications. It has to be done however by injectors with considerable knowledge of back anatomy and botulinum toxin injection technique. It is currently not a FDA approved indication.

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

Shingles (Herpes Zoster) results from reactivation of childhood chicken pox virus in the later years of life. The disease starts with eruption of small vesicles over the skin with a typical distribution pattern along the course of the nerve routes or peripheral nerves. Back, chest and limbs are commonly involved but, in some cases, eruptions occur on the face. In the early stage, when vesicles have erupted on the skin, itch is the most disturbing complaint. After a few weeks, the vesicles dry up and leave scars and cause skin discoloration. Some patients with shingles may develop pain either during the acute phase or more often after skin lesions heal (post-herpetic

neuralgia). The pain is often described as severe, sharp and jabbing and is felt in the distribution of the involved nerves. In some patients, large parts of the body can be affected. The percentage of patients who develop pain after shingles is highly dependent on the age at the onset of their symptoms; it is 5% among individuals younger than 60% and 20% among patients who are 80 years of age or older [28]. Severity of the initial pain, presence of another type of neuropathy at the time of shingle's skin lesions and slow clearance of shingle's virus from the saliva also correlate with higher incidence of post-herpetic neuralgia (PHN) [29–31].

Vaccination with the newer vaccine against shingles (Shingrix) is more than 90% effective in preventing shingles and reducing the incidence of post-herpetic neuralgia. Treatment with steroids can reduce the pain during the acute phase, but does not reduce the incidence of developing PHN [32]. Early antiviral therapy (treatment against shingle's virus) reduces the risk of developing neuralgia after shingles [33]. Pain of shingles may last for months or even years and can severely incapacitate the affected patient. Therefore employing a treatment approach with low side effect profile is desirable in order to properly manage the post-herpetic neuralgia.

Treatment

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

Botulinum Toxin Therapy in PHN

Animal studies and studies of human volunteers have shown that injection of botulinum toxins into or under the skin alleviates experimentally induced pain [34, 35]. This pain relieving effect of the BoNTs is attributed to the inhibitory effect of the toxin upon pain transmitters such as glutamate, substance p and Calcitonin Gene-related peptide (CGRP) [36, 37].

Several studies have reported the efficacy of botulinum toxin treatment in PHN. Among them are two high quality, double-blind, placebo-controlled, class I investigations (see definition of study classes in Chap. 3) that have demonstrated substantial improvement of pain in a high percentage of patients after injection of botulinum toxin injection under skin at painful areas [38, 39]. One study used Botox and the other a Chinese Botulinum toxin A (Prosigne) similar to Botox. In each patient, 12–20 sites were injected. Botulinum toxin therapy also improved patients' sleep in patients with PDN. The patients in the toxin group also used less opioids for pain control. This experience is shared by several other investigators who found similar results in the open label (not blinded) observations [40, 41]. In a recent study, investigators found that injection of botulinum toxin into the skin relieved pain both during the active phase of the infection and after infection (PHN), but it was more effective in the latter (PHN) [42]. Another study, through meta-analysis (a sophisticated statistical method), compared the effectiveness of botulinum toxin therapy injection with lidocaine injection in a group of patients with PHN. Investigators of this study, reviewed data from 7 high quality reported studies on this subject comprising 742 patients. They found that the efficacy rate (analgesic effect) was significantly higher in the group that had received botulinum toxin injections. There was no difference between the two groups regarding adverse effects [43].

The injections are given through a short (¾ in.), thin (gauge 30) needle. Since injections are uncomfortable due to skin sensitivity, an anaesthetic cream (Emla) may be applied an hour before the injections. The skin may be further numbed by an anaesthetic spray during the injections. The Botox dose per injection site is small, 2.5–5 units, for a total dose of 20–200 units depending on the extent of skin involvement. The pain relieving effect of Botox appears in 3–5 days and can last for 3 or more months. If shingles involves the face, the dose and number of injections need to be limited to a minimum in order to avoid facial weakness. This is, however, an uncommon side effect since the dose per site is small usually 2–2.5 units and injections are superficial. The facial weakness, if it develops, is mild and usually disappears within 2–3 months.

Sample Case

A 62-year-old female presented with severe pain behind the left ear of nearly 2 years duration. Two years ago, she had developed shingles which was characterized by skin lesions in the back of the head and behind the left ear. The affected area was painful and the pain was intensified by the passage of time. She described the pain

as jabbing and stabbing, resulting in loss of sleep, causing marked apprehension in anticipation of the next bout. Some episodes were described as "torture and unbearable." Treatment with a medication against herpes virus (acyclovir) improved the skin lesions but did not alter the pain. More severe bouts of pain were followed by disabling headaches. Painkillers such as gabapentin, pregabalin and oxycodone (narcotic) offered little help.

The patient was referred to Yale University Botulinum Toxin Clinic where her examination showed residual scars of zoster infection behind her left ear. The skin in this area was sensitive to touch. A total of 48 units of Botox was injected in a grid-like pattern under the skin, behind the left ear, at 16 points (3 units/point), using a thin 30-gauge needle (Fig. 5.5). The Botox dilution was 100 units per 2 cc of saline. Patient reported a sharp drop in pain frequency and intensity 5 days after the injections. The pain then completely disappeared at week 2 post-injection, but gradually returned at 2.5 months post-injection. Over the next 2 years following the first treatment, patient received Botox injections every 3–4 months. During the third year, pain relief after Botox injections lasted 6 months. In her last follow up (4 years after the first treatment), she had no pain for 9 months and the returned pain was described as subtle and insignificant. She was very pleased with the outcome.

Trigeminal Neuralgia (TN)

This term applies to facial pain that is felt in the distribution of trigeminal nerve. The trigeminal nerve, the fifth cranial nerve (one of 12 cranial nerves that supply the eyes, tongue, throat, head and face), is a pure sensory nerve. It supplies sensation of

Fig. 5.5 Site of Botox injections for the above described patient with post-herpetic neuralgia. (Drawing, courtesy of Damoun Safarpour M.D.)

the upper, middle and lower face regions. Face pain in TN is sharp, jabbing and short lasting often occurring several times during the day and unnerves the patient. It is usually felt on one side of the face sparing the forehead. In some cases, pain radiates to the gums and inside the mouth.

Trigeminal neuralgia is usually a problem of middle or old age and rarely affects young people. The age of onset in most patients is between 50 and 60 years. It has a prevalence of 4/100,000 in the US [44]. If a young person develops TN, multiple sclerosis or a tumor at the base of the brain (brain stem) should to be suspected. Among older individuals, the cause of TN in some patients is compression of a small blood vessel against the trigeminal nerve deep in the brain, Treatment is medical or, in some cases surgical. Medical treatment includes medications which are commonly used for treatment of epilepsy that slow down sensory nerve conduction and have analgesic effect. The commonly used such drugs are phenytoin, carbamazepine (tegretol), gabapentin (neurontin), pregabaline, levitracetam and lamotrigine. Although partially effective, side effects are not uncommon (dizziness, nausea, confusion) leading to unsuccessful longterm use.

The most popular surgery for TN is called microvascular surgery. In this procedure the surgeon opens the back of the skull and separates nerve from the culprit blood vessel that pressing against it. It is effective, but the pain can recur after several years. Furthermore, the surgical procedure is a major task with potential serious side effects such as loss of hearing and balance. Radiofrequency stimulation and Gamma knife surgery are also performed with some degree of success in patients with TN. Peripheral nerve electrical stimulation, deep brain stimulation and transcranial magnetic stimulation are under investigation. In a few patients, focused ultrasound relieved the pain by causing microlesions deep in the specific sensory part of the brain [45].

Botulinum Toxin Treatment

Two high quality class I (see definition in Chap. 3), double-blind, placebo-controlled studies have demonstrated the efficacy of botulinum toxin therapy in management of trigeminal neuralgia [46, 47]. Both investigations used a Chinese botulinum toxin type A similar to Botox (Prosigne). Prosigne's units are believed to approximate Botox's units. The investigators in both studies injected the involved skin of the face in a grid-like pattern at 12–16 sites. Injections not only improved pain but also significantly improved the patients' quality of life. One of these two studies [47] compared the results of low dose (25 units) with high dose (75 units) of Prosigne for pain relief in TN. The authors concluded that 25 units is as effective as 75 units for pain relief and suggested using the low dose of 25 units in order to avoid facial weakness. The author of this chapter has injected 8 patients suffering from TN with Botox using a method similar to that described above. Five of the eight patients experienced a satisfactory response.

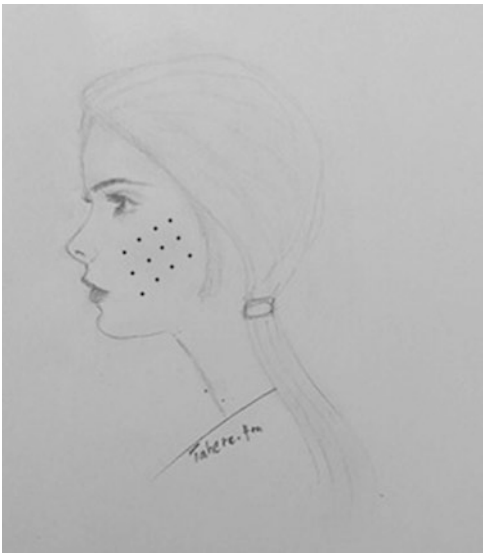

Fig. 5.6 The sites of Botox injections in author's patient with trigeminal neuralgia. (Drawing, courtesy of Tahereh Mousavi, M.D.)

Sample Case

A 41-year old female complained of severe, intermittent jabbing pain in the left face for 9 months. The pain involved mainly the middle of the face, but often radiated to the left ear. It lasted 5–30 s, but recurred frequently, sometimes 5–10 times/day. Treatment with different painkillers offered no relief. Patient stated the sharp pain often depresses her as there seems to be no remedy for it. Injection of Botox into the left side of her face at 12 points (2 units per point- Fig. 5.6) resulted in marked reduction of pain frequency (from 3 to 4/day to 1 to 2/month). The recurring pain was considerably lighter in intensity compared to its predecessors. Repeated injections every 4 months had the same effect.

Diabetic Neuropathy(DN)

Neuropathy means a diseased peripheral nerve. Diabetes can damage peripheral nerves and cause diabetic neuropathy. Diabetic neuropathy affects 25–26% of individuals with type 2 (late onset) and 16% of individuals with type 1 (early onset) diabetes [48]. Patients with DN complain of pain, numbness and, in advanced cases, weakness in the feet or hands. These symptoms are more prominent in the lower limbs. The skin in the affected areas is sensitive to touch (hyperesthesia) and sometimes touch evokes pain (allodynia). Pain may develop spontaneously and interfere with patients' rest and sleep. The pain of diabetic neuropathy has the characteristic of a neuropathic pain. Neuropathic pain is sharp and burning and is often associated with allodynia (skin sensitivity to touch). Areas most commonly affected in diabetic

neuropathy are top of the foot and toes. Painful diabetic neuropathy (PDN) affects 20–24% of the patients with diabetes [49].

On examination, the patients often demonstrate decreased sensations to heat, cold, touch and position in the affected limbs. Diabetic neuropathy is usually bilateral and involves both sides. The symptoms are more severe in the distal parts of the lower limbs, feet and toes. There may be discoloration of the skin overlying the affected areas.

Treatment of diabetic neuropathy consists of avoiding sugar, lowering blood sugar levels with medications and treating pain when present. Mild cases of painful neuropathy can be managed by over the counter pain killers, whereas more severe cases require prescribed medications with recognized efficacy in neuropathic pain syndromes. Gabapentinoids (gabapentin, pregabalin), tricyclic antidepressants (amitriptyline), as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine) are generally accepted as the first line of drugs for PDN [50]. Canadian guidelines (Diabetes Canada-DC) recommends pregabalin to be used before other agents [51]. Sodium channel blockers, such as carbamazepine, oxcarbazepine, lamotrigine, and lacosamide are also recommended by AAN as additional first line drugs [52]. Unfortunately, despite availability of the above-mentioned drugs for neuropathic pain, recalcitrant pain in DPN is not uncommon and when present, impairs the patients' quality of life significantly.

Botulinum Toxin Therapy for PDN

Efficacy of botulinum toxins against pain in PDN has been investigated in four double-blind, placebo-controlled studies [53–56]. Injections were performed with a thin and short needle (less than 1 in. in length, gauge 27.5 or 30) in a gride-like pattern covering the dorsum (top) of the foot (Fig. 5.7). The number of injected sites varied from 12 to 15 in different studies. Some studies used Botox, whereas others used Dysport. Dysport is another type A botulinum toxin similar to Botox. However, the unit strength of the two toxins is different. As described earlier, each unit of Botox approximates 2.5–3 units of Dysport. The dose per injection site was small, 2.5–5 units for Botox. In one study, toxin therapy not only improved pain but also improved the patients' sleep and quality of life [55]. In another recent study [57], injection of 30–100 units of Botulinum toxin A into calf muscles or flexors of the toes significantly improved muscle cramps in PDN, an effect that persisted for 20 weeks with repeated injections (every 3–4 months).

Plantar Fasciitis

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

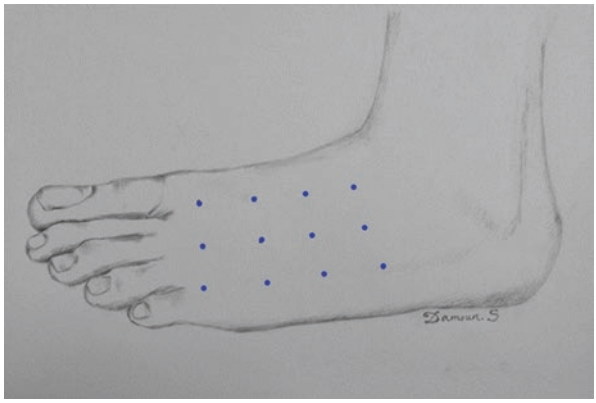

Fig. 5.7 Technique of skin injection for painful peripheral neuropathy in diabetic patients (Yuan and coworkers) [53]. Injections were performed on both feet. (Drawing, courtesy of Damoun Safarpour, M.D.)

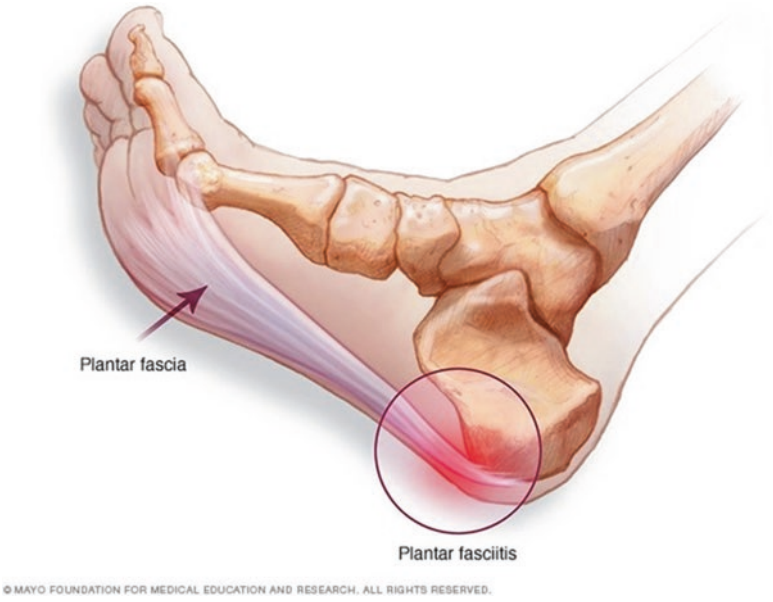

Fig. 5.8 Planter fascia and the area of pain (in red) in plantar fasciitis. (Courtesy of Mayo Foundation)

layer of fibrous tissue (just under the skin of the sole of the foot) that connects the medial part of the heel to the base of the toes (Fig. 5.8). It is thickest, close to its origin at the heel and it thins out as it approaches the toes. When it gets close to the toes, plantar fascia divides into five segments each connecting to the base of one toe. Under the PF, are located three muscles that flex the toes, one for three middle toes, one for the big toe and one for the small toe.

Damaged plantar fascia causes pain that is felt most often in the heel(s), but also sometimes at the bottom of the feet. Pain can be felt during exertion or after a period

of rest. It can be severe, impair the quality of life and interfere with sleep. In many patients, stopping the culprit activity (running, long distance walking, heavy lifting) improves the condition and the pain gradually subsides. Other patients with plantar fasciitis, however, may continue experiencing pain despite stopping the responsible activity or a job that requires continuing heavy foot works such as football or running. Plantar fasciitis affects 10% of all runners and over two million people in the US [58].

Treatment of PF starts with simple measures such as stretching, taping, night splints, orthosis, non-steroidal, anti-inflammatory medications. In more persistent cases, steroid injections, ultrasound therapy, application of shock waves, acupuncture and cryosurgery (with freezing probes) are used. Unfortunately, the positive effect of these measures is often short lived. Furthermore, some of these therapeutic approaches are painful and hard to tolerate (i.e. shock wave therapy), while injection of steroids may cause rupture of the plantar fascia and make the situation more complicated. Clearly, an effective and safe treatment approach with less side effects is desirable for management of severe forms of PF.

Botox Treatment of Plantar Fasciitis (PF)

In 2005, author of this chapter and his colleagues conducted and published the results of the first prospective, placebo-controlled, double-blinded investigation on the efficacy of Botox in plantar fasciitis at the Walter Reed Army Medical Center (WRAMC) in Washington D.C. [59]. Twenty-seven patients with plantar fasciitis and chronic symptoms (lasting >6 months) completed the study. Study subjects received either Botox (70 units) or placebo (saline), 0.7 cc into two sites: (1) medial part of the heal(s), origin of plantar fascia 40 units of Botox or 0.4 cc of saline (2) into the bottom of the foot, at mid-point, between the heal and base of the toes (if Botox 30 units, if saline 0.3 cc) (Fig. 5.9).

Efficacy of the treatment was measured at 3 and 8 weeks following injections. The group that received Botox injections improved in several measures compared to the placebo: Maryland Foot Score ($P = 0.001$), Pain Relief measured by Visual Analog Scale, on the scale of 0–10 ($P < 0.0005$), and the Pressure Algometry Response ($P = 0.003$); in clinical research; P scores of less than 0.05 are considered statistically significant. No side effects were noted. Later, our group found through experience that adding an additional injection into the soleus muscle which is often tight in plantar fasciitis leads to more alleviation of pain (Fig. 5.10).

In 2010, Huang and co-workers [60], using a similar technique and a total dose of 50 units (Botox), reported very similar results in a blinded study of 50 patients with plantar fasciitis. Díaz-Llopis and coworkers [61] compared the efficacy of Botox injection in plantar fasciitis with a combined steroid (betamethasone) and lidocaine injection in plantar fasciitis. One month after injections, both groups described pain relief which was more notable among patients who had received Botox. At 6 months post-treatment, patients who had received Botox were still satisfied with the level of pain relief, whereas patients who had received steroids

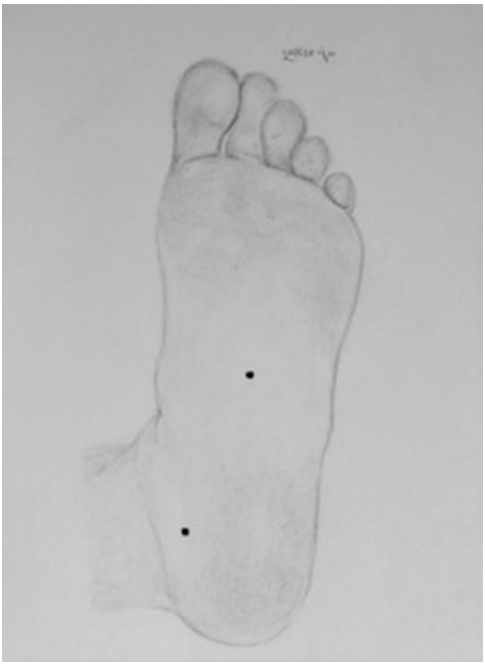

Fig. 5.9 Recommended sites of Botox injection in plantar fasciitis [59]. (Drawing, courtesy of Tahereh Mousavi, M.D.)

experienced recurrent pain. Similar result regarding superiority of Botox to steroid was noted in another comparative study where, in addition to heal injection authors also injected into the soleus muscle [62]. In 2017, improvement of pain and foot function was reported in patients with PF following Xeomin (another type of botulinum toxin A similar to Botox) injections into the painful sites of the foot [63]. The units of the Botox and Xeomin have approximately the same strength. In a more recent study [64], investigators compared the result of Botox injection with injection of an steroid (dexamethasone) or an anesthetic (lidocain) in patients with plantar fasciitis. Six months after injection, all three treatments improved pain in planter fasciitis and there was no significant difference between the three. This study did not include additional soleus injection. Considering the results of the studies cited above, botulinum toxin A (Botox or Xeomin) injections can relieve pain in plantar fasciitis and this treatment seems to be more effective than steroid injections if injection of the soleus muscle is included among the injection sites. Botox treatment seems to be safer and has less side effects than steroid therapy.

Sample Case

A 73 year-old man had noted discomfort at the bottom of his feet, 7–8 years prior to a visit to the Yale Botulinum Toxin Treatment clinic. He was an avid tennis player who felt the most foot discomfort on the days that he played longer games. The

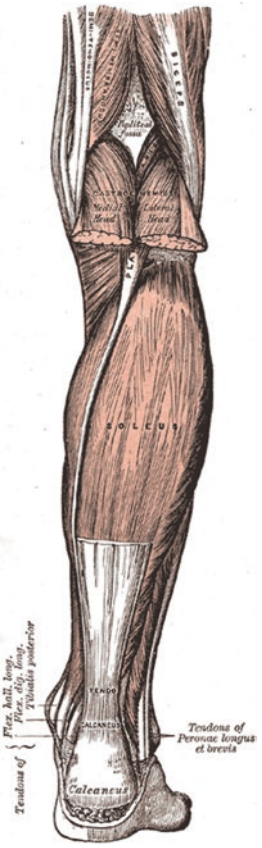

Fig. 5.10 Soleus muscle can be injected on the back of the calf. The injector should avoid injecting Achilles tendon (colored white below soleus) which easily ruptures. (Figure from Gray's anatomy provided by Wikimedia under Creative Commons Attribution-Share Alike 4.0 license)

discomfort gradually changed to pain which was felt at the heels and around the medial part of both feet. Over the years, he had tried a variety of treatments including stretching, orthosis, night splints, non-steroidal anti-inflammatory drugs, sessions of acupuncture and steroid injections. The latter two had helped some, but the results were short lived. He stated having more "bad" days recently during which the heel pain was severe and quite uncomfortable.

His neurological examination was normal. Botox was injected into both feet using the methodology described above. A total of 70 units was injected −40 units close to the heel and 30 units at the bottom of the foot (Fig. 5.9). Within days, the patient reported significant improvement of his heel pain; the pain relief lasted for 7 months. The second treatment also produced pain relief for 7–8 months. For the third and fourth treatments, an additional 30 units of Botox was injected into the soleus muscle which is located at the back of the lower leg and flexes the foot down via its attachment to Achilles tendon (10). It is often found to show increased tone in patients with PF. The third and fourth injections provided longer pain reliefs (9–10 months). Patient reported no side effects.

Pain After Trauma to the Peripheral Nerves (Post-traumatic Neuralgia)

Trauma to the peripheral nerves can cause sustained pain in the distribution of the injured nerves that sometimes, due to the intensity of pain, incapacitates the patient.

Case Report

A 56-year-old woman was referred to the Yale Botulinum Toxin Treatment Clinic for evaluation of severe post-traumatic 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 (touch perceived as pain) developed over the lateral malleolus (bone at the ankle) extending up 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 coltran gel. In 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 (tough causing pain) 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 the ankle (Fig. 5.11).

OnabotulinumtoxinA (ona-A) was injected subcutaneously into the dorsolateral aspect of the right foot (50 units; 20 sites—grid pattern) including the region of lateral malleolus. 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, 3 months later (VAS score went down to 1–2) 6 months later. Patient state that 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.

Based on anecdotal observations such as the patient described above, and the animal studies that illustrated the analgesic effect of botulinum toxins in animal models [6–15], investigators began to assess the efficacy of botulinum toxin

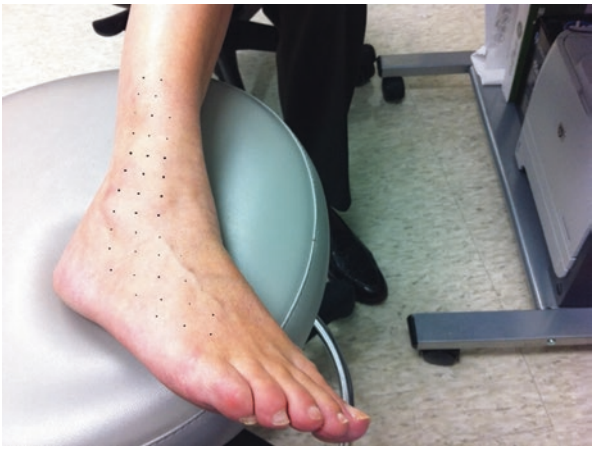

Fig. 5.11 Site of Botox injections for post-traumatic neuralgia. Darker dots illustrates areas of more intense pain. (From author's personal collection)

injections in human post-traumatic painful neuropathies through high quality studies. In 2008, Dr Ranoux and co-workers from France [65] studied 25 patients using a double-blind, placebo-controlled protocol. Patients had both surgical and non-surgical trauma to a single peripheral nerve. Botox injection were performed into the skin with a small needle over the area of pain at 20 points, 1 cm apart. The total dose per session ranged from 20 to 190 units based on the extent of the painful areas. The pain intensity started to decrease from 2 weeks post-injection in favor of Botox (versus saline/placebo) and the improvement lasted until week 14 ($P = 0.03$). No patient reported any side effects except seconds of pain at the time of injection. In 2017, the same group [66] looked at efficacy of repeated Botox injections in 64 patients (34 in BoNT group, 32 in saline group) with neuropathic pain at three research centers. Patients had two injections, 12 weeks apart. The method of injections was the same as that of the first study. The patient's response was evaluated at 4, 6, 12, 16 and 24 weeks after the first injection. Compared to placebo, self-reported pain intensity was significantly decreased after week 1 following after Botox injection and remained significantly decreased in each of the subsequent weeks through the duration of the study. The results of these two studies strongly support the usefulness of Botox injections into the skin in patients suffering from severe pain after trauma to the peripheral nerves.

Neuropathic Pain Secondary to Spinal Cord Injury

Han and coworkers [67] 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 200 units of a South Korean type A botulinum toxin (Meditoxin, South Korea). The toxin was delivered in a checkerboard pattern under the skin at the region of pain. At 4 and 8 weeks

post-injection, 55% and 45% of the patients reported pain relief of 20% or greater in the toxin injected group versus 15% and 10% in the placebo group. The quality of life was also improved more in the toxin injected group. No motor or sensory deficit was noted after botulinum toxin injections. Chun and colleagues [68] replicated these results in a smaller number of eight patients with local pain after spinal cord injury at lower thoracic and upper lumbar areas. In their study, Botox injections under the skin were also compared with the saline injections. The total injected dose of Botox was 200 units.

The above mentioned human observations on the analgesic effect of BoNT therapy for post-traumatic neuralgia in neuropathic pain after spinal cord injury are supported also in animal models of spinal cord injury with post-traumatic neuralgia [69].

Piriformis Syndrome (PS)

Piriformis syndrome is a clinical condition characterized by deep pain in the buttock related to tightness of piriformis muscle which is located deep in the buttock under gluteal muscles (large buttock muscles). Tightness of the triangular piriformis muscle can cause pain deep in the buttock due to its proximity to the roots of the sciatic nerve. The pain of piriformis muscle can be confused sometimes with low back pain due to a dislocated disc in the spinal column or with sciatica that results from irritation of the sciatic nerve itself in the thigh.

Diagnosis of piriformis syndrome is often difficult due to complexity of the involved anatomy. In mild cases, treatment with non-steroidal analgesics is helpful. For recalcitrant pain more aggressive treatment is required.

Botox injection into piriformis muscle has been shown to improve pain resulting from the piriformis syndrome. The largest placebo-controlled, blinded study was conducted by Fishman and co-workers who compared the results of Botox, lidocaine and placebo injections into the piriformis muscle of patients affected by PS. After injections, pain relief was noted in 67%, 32% and 6% of the three groups, respectively [70]. The technique of injection is laborious and needs to be performed under electromyographic guidance to ensure proper insertion of the injecting needle. Electromyography records the electrical activity of the muscle and, in case of piriformis syndrome, often demonstrates abnormal increased activity of this muscle at rest. For injection, a special hollow needle is used that both records the muscle activity and allows injection of botulinum toxin through its core. Unlike for most indications of botulinum toxin therapy that utilize a short needle (¾ to 1 in.), a long needle, 4.5–5 in., is needed for injections in PS in order to reach the deeply located piriformis muscle (Fig. 5.12). For Botox, usually a dose of 100 units is delivered in a single injection.

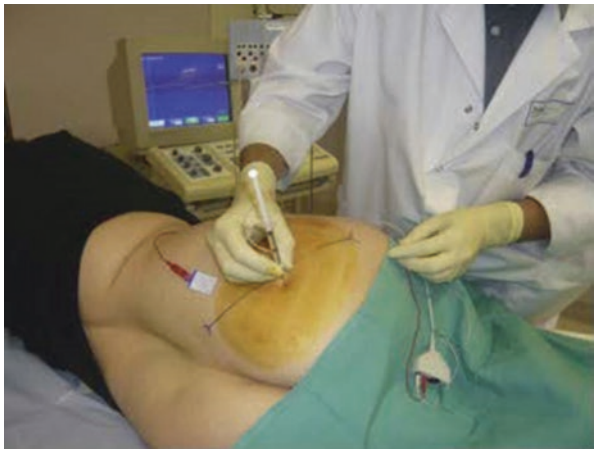

Fig. 5.12 Technique of botulinum toxin injection into the piriformis muscle. (Michel and co-workers 2013 [71]—Reproduced under https://creativecommons.org/licences/by/4.0. Courtesy of publisher Elsevier Masson SAS [71])

In a recent double -blind, placebo-controlled study of 84 patients, authors compared the results of botulinum toxin injection (under ultrasound guidance) with combined injection of ozone and steroids into the priformis muscle. Both effectively reduced the pain days after injection, but combination of ozone and steroid had more analgesic effect in short term. However, botulinum toxin analgesic effect surpassed the effect of combination therapy at 3 and 6 months [72].

There are several other pain syndromes in which there is scientific evidence for efficacy of botulinum toxin therapy. These include pain in arthritis, muscle pain associated with stroke, pain associated with involuntary neck movements (cervical dystonia), bladder and pelvic pain and pain associated with certain childhood surgeries. These are discussed in other chapters of this book.

Conclusion

Neuropathic pain (NP) comprise a large group of pain disorders that results from disturbance of peripheral nerves by trauma, pressure, infection and other factors. Less commonly, neuropathic pain is due to spinal cord injury (central pain). Although FDA has not yet approved botulinum toxin therapy for any of the categories of neuropathic pain discussed in this chapter, evidence from high quality studies strongly suggests efficacy of botulinum toxin therapy in several NP categories. In clinical medicine, insurance companies sometimes approve the use of a non-FDA approved drug based on strong evidence presented from published high quality (double-blind, placebo-controlled) studies.

References

1. 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.
2. Yong RJ, Mullins PM, Bhattacharyya N. Prevalence of chronic pain among adults in the United States. Pain. 2022 Feb 1;163(2):e328–32. https://doi.org/10.1097/j.pain.0000000000002291.
3. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10(4):287–333. https://doi.org/10.1016/j.ejpain.2005.06.009.
4. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021 May 29;397(10289):2082–97. https://doi.org/10.1016/S0140-6736(21)00393-7. PMID: 34062143.
5. Relieving pain in America a blueprint for transforming prevention, care, education, and research. Reli Pain Am A Bluepr Transform Prev Care Educ Res. 2011;26:1–364. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education.
6. Cui M, Khanijou S, Rubino J, et al. Subcutaneous administration of botulinum toxin a reduces formalin-induced pain. Pain. 2004;107:125–33.
7. Marino MJ, Terashima T, Steinauer JJ, et al. Botulinum toxin B in the sensory afferent: transmitter release, spinal activation, and pain behavior. Pain. 2014;155:674–84.
8. Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to clostridium botulinum neurotoxins. Toxicon. 2000;38:245–58.
9. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int. 2012 July;61(2):236–9. https://doi.org/10.1016/j.neuint.2012.05.001.
10. 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 Feb;85(2):209–14. https://doi.org/10.1139/y07-018.
11. 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.
12. 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.
13. 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.
14. 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 Sept 1;358:137–45. https://doi.org/10.1016/j.neuroscience.2017.06.040. Epub 2017 July 1.
15. Tang M, Meng J, Wang J. New engineered-botulinum toxins inhibit the release of pain-related mediators. Int J Mol Sci. 2019 Dec 30;21(1):262. https://doi.org/10.3390/ijms21010262. PMID: 31906003; PMCID: PMC6981458.
16. Andersson GBJ. Epidemiological features of chronic low-back pain. Lancet. 1999;354:581–5.
17. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. Lancet. 2012 Feb 4;379(9814):482–91. https://doi.org/10.1016/S0140-6736(11)60610-7. Epub 2011 Oct 6.
18. Knezevic NN, Candido KD, Vlaeyen JWS, Van Zundert J, Cohen SP. Low back pain. Lancet. 2021 July 3;398(10294):78–92. https://doi.org/10.1016/S0140-6736(21)00733-9. Epub 2021 June 8.
19. 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.

20. Machado D, Kumar A, Jabbari B. Abobotulinum toxin A in the treatment of chronic low back pain. Toxins (Basel). 2016, Dec 15;8(12):pii: E374.
21. 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 May–June;7(3):260–4. https://doi.org/10.1111/j.1526-4637.2006.00147.x.
22. 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 Fall;1(2):77–80. https://doi.org/10.5812/kowsar.22287523.1845. Epub 2011 Sept 26. PMID: 25729661; PMCID: PMC4335729.
23. Sahoo J, Jena D, Viswanath A, Barman A. Injection botulinum toxin A in treatment of resistant chronic low back pain: a prospective open-label study. Cureus. 2021 Sept 8;13(9):e17811. https://doi.org/10.7759/cureus.17811. PMID: 34660021; PMCID: PMC8500249.
24. 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 Nov 15;18(1):454. https://doi.org/10.1186/s12891-017-1816-6. PMID: 29141611; PMCID: PMC5688690.
25. 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 May–June;35(3):255–60. https://doi.org/10.1097/AAP.0b013e3181d23241.
26. 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):1639–43. https://doi.org/10.1212/01.wnl.0000336535.27773.c0.
27. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. Neurology. 2008 Nov 11;71(20):1634–8. https://doi.org/10.1212/01.wnl.0000336533.19610.1b.
28. 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.
29. Thyregod HG, Rowbotham MC, Peters M, Possehn J, Berro M, Petersen KL. Natural history of pain following herpes zoster. Pain. 2007 Mar;128(1–2):148–56. https://doi.org/10.1016/j.pain.2006.09.021. Epub 2006 Oct 27. PMID: 17070998; PMCID: PMC1905461.
30. Baron R, Haendler G, Schulte H. Afferent large fiber polyneuropathy predicts the development of postherpetic neuralgia. Pain. 1997 Nov;73(2):231–8. https://doi.org/10.1016/S0304-3959(97)00105-X.
31. 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 Nov;91(11):1995–2000. https://doi.org/10.1002/jmv.25543. Epub 2019 July 23.
32. 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 Sept 1;125(5):376–83. https://doi.org/10.7326/0003-4819-125-5-199609010-00004.
33. 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 Feb;22(2):341–7. https://doi.org/10.1093/clinids/22.2.341.
34. 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 Dec 15;423:86–97. https://doi.org/10.1016/j.neuroscience.2019.10.007. Epub 2019 Nov 6. Erratum in: Neuroscience. 2020 June 15;437:256.
35. 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 Aug 15;357:197–207. https://doi.org/10.1016/j.neuroscience.2017.06.004. Epub 2017 June 10.

36. Kim DW, Lee SK, Ahnn J. Botulinum toxin as a pain killer: players and actions in Antinociception. Toxins (Basel). 2015 June 30;7(7):2435–53. https://doi.org/10.3390/toxins7072435. PMID: 26134255; PMCID: PMC4516922.
37. 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 May-June;19(3):126–32. https://doi.org/10.1155/2014/410415. PMID: 24851237; PMCID: PMC4158957.
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;11:1827–33.
39. 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.
40. 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 July;66(7):48–9.
41. Ding XD, Zhong J, Liu YP, Chen HX. Botulinum as a toxin for treating post-herpetic neuralgia. Iran J Public Health. 2017 May;46(5):608–11. PMID: 28560190; PMCID: PMC5442272.
42. Peng F, Xia TB. Effects of intradermal botulinum toxin injections on herpes zoster related neuralgia. Infect Drug Resist. 2023 Apr 12;16:2159–65. https://doi.org/10.2147/IDR.S401972. PMID: 37077249; PMCID: PMC10106788.
43. 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 Feb;19(2):1058–64. https://doi.org/10.3892/etm.2019.8301. Epub 2019 Dec 9. PMID: 32010269; PMCID: PMC6966161.
44. 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.
45. Gallay MN, Moser D, Jeanmonod D. MR-guided focused ultrasound central lateral thalamotomy for trigeminal neuralgia. Single center experience. Front Neurol. 2020 Apr 17;11:271. https://doi.org/10.3389/fneur.2020.00271. PMID: 32425870; PMCID: PMC7212452.
46. Wu CJ, Lian YJ, Zhang YK, et al. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32:443–50.
47. Zhang H, Lian Y, Ma Y, et al. Two doses of botulinum toxin type a for the treatment of trigeminal neuralgia: observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. J Headache Pain. 2014;15(1):65.
48. Barrett AM, Lucero MA, Le T, Robinson RL, Dworkin RH, Chappell AS. Epidemiology, public health burden, and treatment of diabetic neuropathic pain: a review. Pain Med. 2007;8(Suppl 2):S50–62. Review.
49. Stewart WF, Ricci JA, Chee E, Hirsch AG, Brandenburg NA. Lost productive time and costs due to diabetes and diabetic neuropathic pain in the US workforce. J Occup Environ Med. 2007 June;49(6):672–9. https://doi.org/10.1097/JOM.0b013e318065b83a.
50. Preston FG, Riley DR, Azmi S, Alam U. Painful diabetic peripheral neuropathy: practical guidance and challenges for clinical management. Diabetes Metab Syndr Obes. 2023 June 2;16:1595–612. https://doi.org/10.2147/DMSO.S370050. PMID: 37288250; PMCID: PMC10243347.
51. Diabetes Canada Clinical Practice Guidelines Expert Committee, Bril V, Breiner A, Perkins BA, Zochodne D. Neuropathy. Can J Diabetes. 2018 Apr;42(Suppl 1):S217–21. https://doi.org/10.1016/j.jcjd.2017.10.028.
52. Price R, Smith D, Franklin G, Gronseth G, Pignone M, David WS, Armon C, Perkins BA, Bril V, Rae-Grant A, Halperin J, Licking N, O'Brien MD, Wessels SR, MacGregor LC, Fink K, Harkless LB, Colbert L, Callaghan BC. Oral and topical treatment of painful diabetic polyneuropathy: practice guideline update summary: report of the AAN Guideline Subcommittee. Neurology. 2022 Jan 4;98(1):31–43. https://doi.org/10.1212/WNL.0000000000013038.

53. 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. s2009;72:1473–8.
54. Ghasemi M, Ansari M, Basiri K, et al. The effects of intradermal botulinum toxin type a injections on pain symptoms of patients with diabetic neuropathy. J Res Med Sci. 2014;19:106–11.
55. 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 July 6;18(3):99–107. PMID: 31749930; PMCID: PMC6858596.
56. Taheri M, Sedaghat M, Solhpour A, Rostami P, Safarpour Lima B. The effect of intradermal botulinum toxin a injections on painful diabetic polyneuropathy. Diabetes Metab Syndr. 2020 Nov–Dec;14(6):1823–8. https://doi.org/10.1016/j.dsx.2020.09.019. Epub 2020 Sept 14.
57. 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 Nov;84(5):674–82. https://doi.org/10.1002/ana.25340. Epub 2018 Oct 16.
58. Kibler WB, Goldberg C, Chandler TJ. Functional biomechanical deficits in running athlitis with plantar fasciitis. Am J Sports Med. 1991;19:63–71.
59. 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.
60. 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.
61. 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.
62. 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 Jan;34(1):8–14. https://doi.org/10.1177/1071100712460215.
63. Ahmad J, Ahmad SH, Jones K. Treatment of plantar fasciitis with botulinum toxin. Foot Ankle Int. 2017;38:1–7.
64. 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 Mar;42(3):305–13. https://doi.org/10.1177/1071100720961093. Epub 2020 Oct 8.
65. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol. 2008 Sept;64(3):274–83. https://doi.org/10.1002/ana.21427. Erratum in: Ann Neurol. 2009 Mar;65(3):359.
66. 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 May;15(6):555–65. https://doi.org/10.1016/S1474-4422(16)00017-X. Epub 2016 Mar 2.
67. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol. 2016 Apr;79(4):569–78. https://doi.org/10.1002/ana.24605. Epub 2016 Feb 16. PMID: 26814620; PMCID: PMC4825405.
68. 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 Sept 18;5:77. https://doi.org/10.1038/s41394-019-0221-9. PMID: 31632735; PMCID: PMC6786298.

69. 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 July 31;12(8):491. doi:https://doi.org/10.3390/toxins12080491. PMID: 32751937; PMCID: PMC7472120.
70. Fishman LM, Anderson C, Rosner B. BOTOX and physical therapy in the treatment of piriformis syndrome. Am J Phys Med Rehabil. 2002;81:936–42.
71. 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 July;56(5):371–83. https://doi.org/10.1016/j.rehab.2013.04.003. Epub 2013 Apr 25.
72. Elsawy AGS, Ameer AH, Gazar YA, Allam AE, Chan SM, Chen SY, Hou JD, Tai YT, Lin JA, Galluccio F, Nada DW, Esmat A. Efficacy of ultrasound-guided injection of botulinum toxin, ozone, and lidocaine in piriformis syndrome. Healthcare (Basel). 2022 Dec 28;11(1):95. https://doi.org/10.3390/healthcare11010095. PMID: 36611554; PMCID: PMC9818865.