Chapter 19
Botulinum Toxin Therapy-Future Perspectives

Abstract New potential applications for botulinum neurotoxin (BoNT) therapy are constantly emerging through the expanding literature in the field of clinical toxicology. In this chapter, we discuss potential indications for botulinum neurotoxin treatment in five major fields of medicine: Psychiatry (depression), cardiology (irregular heartbeats, atrial fibrillation), cancer related disorders (cancer related pain, prevention of post-surgical and post radiation pain, prevention of esophageal narrowing after surgery for esophagal cancer, prevention of parotid gland fistula and cyst formation after parotid cancer surgery and alleviating excessive face sweating and severe jaw pain after first bite following parotid gland surgery). In dermatology, there is evidence that local botulinum toxin injections can help psoriasis and recalcitrant itch as well as palm pain and vascular palm problems associated with Raynaud syndrome. In pain medicine, botulinum toxin injections can help to reduce teeth grinding and associated pain, jaw pain from temporomandibular disorder, pain and discomfort of anal fissure.

Keywords Botulinum toxin · Botulinum neurotoxin · Cancer related pain · Post-surgical pain · Post radiation pain · Neuropathic pain · Atrial fibrillation · Depression · Raynaud syndrome

Introduction

In the preceding chapters, we have discussed clinical conditions in which high quality studies have shown the efficacy of botulinum neurotoxins (BoNTs) in improving the symptoms of various medical disorders. There are many other important clinical conditions in which the preliminary results of BoNT therapy are encouraging, but the proof of efficacy for most of these conditions requires the availability of positive results from well- designed, and high quality clinical trials. These potential indications pertain to medical disorders for which current medical management is challenging and often provides unsatisfactory results. The challenged clinicians, therefore, would welcome alternative treatment approaches, that in addition to

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efficacy, do not require daily use of oral medications or surgery, while producing fewer side effects.

The list of potential indications for BoNT therapy is long and is growing. For this chapter, we have selected potential indications in five major fields of medicine: Psychiatry, cardiology, cancer related disorders and dermatology and pain medicine. Since the first edition of this book which was published 5 years ago, there have been more publications supporting BoNT therapy for these indications. In psychiatry, we will address treatment of depression with botulinum neurotoxins and the possible mechanisms of its effectiveness. In cardiology, there is evidence that careful and titrated injection of botulinum toxins into the surface of the heart (where heart's nerves are located) can improve irregular heartbeats caused by atrial fibrillation. Potential indications in cancer related disorders include treatment of pain after cancer surgery and/or radiation, prevention of esophageal narrowing (stricture) after removal of esophageal cancer, prevention of parotid gland fistula and cyst formation after parotid cancer surgery, as well as excessive face sweating after parotid surgery. In dermatology botulinum toxin injections into the skin may abort recalcitrant itch, improve psoriasis and alleviate palm pain and skin changes in Raynaud syndrome.

Psychiatry: Depression

Severe depression, a major depressive disorder (MDD), is a common disease that affects 5–10% of men and 10–25% of women [1]. Lack of interest and severe depressive mood of the affected patients often lead to an impaired quality of life and ultimately to the patients' functional disability. Medical treatment of depression includes application of several different categories of medication and is beyond the scope of this chapter; this information is available in recent extensive reviews [2]. Although antidepressive medications are effective, their side effects (some severe) limit their use in many patients and it may take 6 weeks before seeing results [2]. Therefore, availability of a mode of treatment that has less side effects, acts faster and does not require daily consumption of medications is highly desirable for treatment of chronic depression.

Following earlier observations that botulinum toxin injections into the forehead muscles for cosmetic reasons, significantly improved mood in some patients [3, 4], researchers began to methodically study the effect of botulinum toxin therapy on severe depression. Over the past 20 years, 6 high quality studies [5–10] have been conducted on the subject of botulinum toxin therapy in depression (Table 19.1). These studies were double—blind and placebo-controlled, i.e. the effect of the injected toxin into the forehead and, in some cases, with additional injections into the muscles over the corner of the eyes was compared with injection of placebo (salt water). Double- blind means that both the injecting physician and the patient were not aware whether the injected material was Botox or salt water in any of the injection sessions. In all studies, the glabellar muscles were included in the plan of injection. Glabella is the forehead region above the nose and between the two eyebrows.

Table 19.1 High quality, double-blind, placebo- controlled studies reported on safety and efficacy of Botox and other type A botulinum toxin injections into the glabellar and forehead muscles of depressed patients

Author and date	#pts	Study design	Toxin type, total dose	Assessment	Results
Vollmer et al. [5]	30	DB, PC	Botox, 26 units	Hamilton depression rating scale-21 (HDRS) at week 6	Significant improvement Botox: 47.1% vs placebo:9.2%
Finzi and Rosenthal [6]	74	DB, PC	Botox, 29–40 units	50% reduction in Montgomery-Asberg depression scale at week 6	Significant improvement Botox: 52% vs placebo: 15%
Magid et al. [7]	30	DB, PC	Botox, 29–30 units	Beck depression scale at week 6	Significant improvement Botox: 55% vs placebo: 5%
Brin et al. [8]	255	DB, PC	Botox, 30 units	Montgomery-Asberg (MA) depression scale assessed every 3 weeks up to 24 weeks	M-A depression scores consistently and significantly improved in Botox group compared to placebo group over 24 weeks (Fig. 19.2)
Zhang et al. [9] Comparing Botox with sertraline	76	DB	Botulinum toxin A from Lanshou-China.:100 units, Sertarline: 50–100 mg	Hamilton depression (HD) scale and Hamilton anxiety (HA) scale-at 12 weeks	In both groups botulinum toxin and sertraline reduced HD and HA scores significantly. Onset of Botox effect was earlier and Botox injections had less side effects
Li et al. [10]	88	DB, PC	Botulinum toxin A from Lanshou institute in China: 100	Hamilton depression scale and Hamilton anxiety scale-12 weeks	Both Hamilton scores improved significantly over 12 weeks compared to placebo

DB double blind, *PC* placebo controlled

It covers a single muscle (procerus) located at midline between the two eyebrows and the two corrugator muscles—one on each side above the most medial part (closest to the nose) of the eyebrows (Fig. 19.1). These muscles are also called frown line muscles as their contraction leads to frowning and pulls the eyebrows together. As can be seen in Table 19.1, Botox injection into the forehead muscles (and in some studies combined with injection at corner of the eyes) significantly improved depression scores in patients who received Botox. This effect was much less noted in the placebo-injected patients. The total dose of Botox used in these studies varied from 30 to 100 units. Each injection site received a small dose of 5 units.

The largest of these six double- blind, placebo- controlled studies on efficacy of botulinum toxins in depression was performed by Brin and coworkers [8]; they

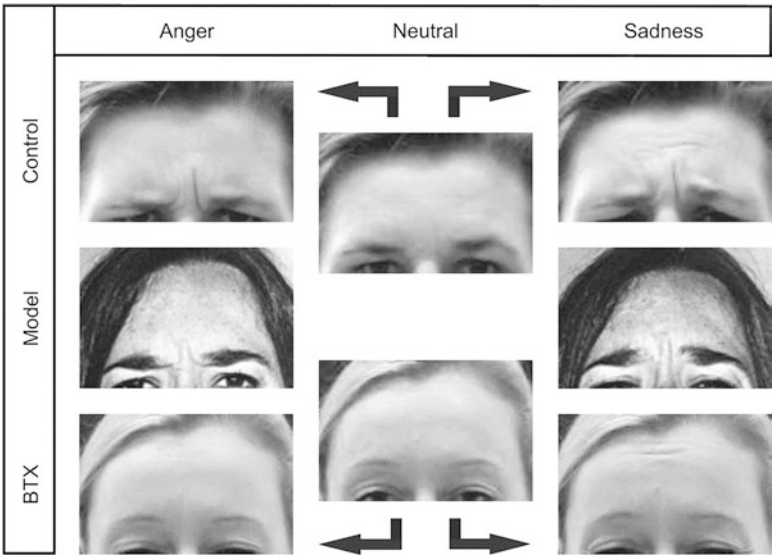

Fig. 19.1 The function of glabellar muscles: frowning during volition (not shown) and during anger and sadness. Lower part of the figure shows the effect after Botox treatment. (From Hennenlotter et al. [4]. Courtesy of Oxford Academic Press)

studied 225 patients. This study was designated as a Phase II clinical trial study (for definition of clinical trials and phases see Chap. 2). A phase II clinical study aims mainly to establish the safety of a new drug, but also to some extent investigates the drug's efficacy. This study demonstrated that repeated Botox injections into the forehead area of depressed patients over 24 weeks was safe and devoid of serious side effects. It also showed that over the period of 24 weeks, at each assessment point (every 3 weeks) (Fig. 19.2). Botox injection of 30 units (total dose) was superior to placebo in improving the patients' depression. A positive Phase II study is a requirement for proceeding to a phase III study, upon the positive results of which, FDA usually approves the drug for clinical use in the US. Phase III studies are large multi-center studies conducted under more stringent regulations.

The positive data from the above mentioned studies (Table 19.1) are supported by further positive data from literature that have shown botulinum toxin therapy can also alleviate depression associated with chronic migraine and Parkinson disease [11, 12]. The theories that how BoNT injection into skin and thin muscles of the forehead (glabellar region) can relieve depression are presented later in this chapter.

Technical Points

Injections are performed with a small needle (gauge 27.5 orvv30) into thin muscles of glabellar and low forehead. Injections are quick and all can be completed within 4–5 min. In very sensitive individuals, the skin may be numbed before injections

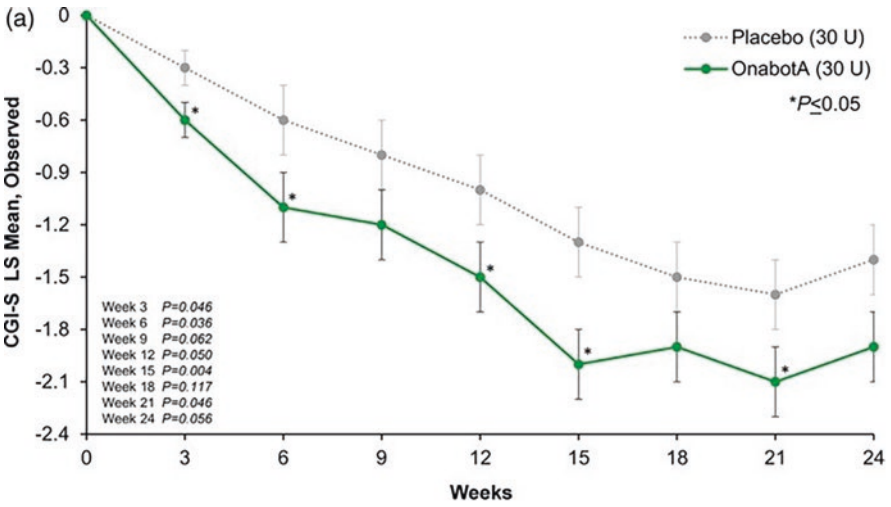

Fig. 19.2 On each assessment point after injections (Botox or placebo), Botox improved the depression scores more than the placebo (green line). (From Brin et al. [8]. Printed with permission from publisher, Wolters Kluwer)

with a topical anesthetic cream an hour before injection (for example, Emla cream). In most patients, however, numbing the injection sites is not necessary. Most studies have used 5–8 injection sites limited to glabellar region(procerus and corrugator muscles) and lower forehead [5–8] (Fig. 19.3). Some investigators include additional injection sites, for instance three additional injections at the corner of each eye [9].

Zhang and co-investigators compared the result of BoNT-A injections (Chinese toxin with units comparable to Botox) with the oral use of antidepressive drug sertraline in 78 patients with depression [9]. The total dose of BoNT-A was 100 units and the total dose of daily sertraline was 50–100 mg/day. BoNT-A was injected into 20 points at the glabellar and low frontal regions as well as both corner of the eyes (5 units/site). Both modes of treatment improved depression with comparable magnitude. The onset of botulinum toxin effect however was earlier. Also, botulinum toxin treatment of depressed patient caused less side effects compared to sertraline therapy (15.4% versus 33%).

Schultze and coworkers [12] performed a meta-analysis of the published data on the role of botulinum toxins in alleviating depression. Meta-analysis is defined as a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive conclusions about that body of research. The authors concluded that despite some methodological limitations, botulinum toxin treatment has shown to be effective for treatment of depression and the road seems to be paved for its use in the field of psychiatry.

How injection of Botox into low frontal region and glabellar muscles (procerus and corrugator) leads to improvement of major depression is difficult to explain.

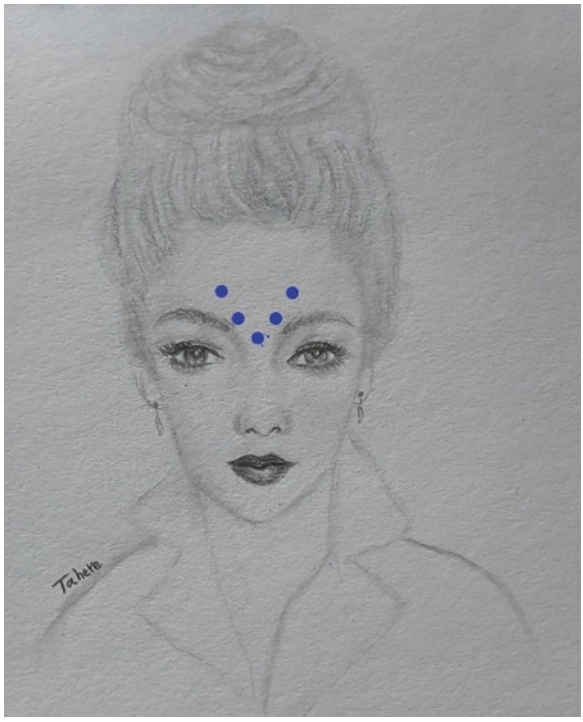

Fig. 19.3 Recommended injection sites of Botox d for treatment of depression per Finzi and Rosenthal, 2014. The injection between two eyebrows is into the procerus muscle that pulls the skin between two eyebrows down. The two infections at the medial border of eyebrows are into the corrugator muscles that bring eyebrows together. Upper injections are into frontalis muscles. (Drawing courtesy of Dr. Tahere Safarpour)

One simple explanation is that improvement of frown lines makes the patients happier and happier patients are less depressed.

Finzi and Rosenthal [6] have proposed that glabellar muscles, as muscles of facial expression, influence the activity of the brain cells in those areas of the brain that are involved in emotions such as temporal lobe and part of frontal lobe (prefrontal cortex -PFC). Another area of the brain which is involved in emotions is called amygdala. Amygdala (meaning almond in Greek) is an almond shape structure that consists of a group of nerve cells located deep in the brain with connections to other areas of the brain that are concerned with emotions. Functional MRI (fMRI) studies have shown frowning, following observing an unpleasant picture is associated with decreased activity in pre-frontal cortex (PFC) and increased activity in amygdala [13]. Antidepressant medications (drugs used for treatment of depression) like paroxetine increase activity of PFC and decrease the activity of amygdala in fMRI. Studies of the brain activity with fMRI have shown that the same thing happens with Botox injection into the glabellar muscles which decreases the tone of glabellar muscles and flattens the frown lines [14] (Fig. 19.2).

Using the criteria of American Academy of Neurology (see Chap. 3 of this book for definition of AAN criteria, study class and efficacy levels), and based on the current published literature that includes one class I [8] and 5 class II [5–7, 9, 10] studies in this area, the efficacy level of Botox therapy for depression would be “B”, i.e. probably effective (a definitely effective designation requires two class I studies) .

So far, most of the reported patients in the high quality studies (Table 19.1) have been women. There is a need for similar studies in male patients. Furthermore, Botox and Chinese toxin (another type A toxin) have been the only two botulinum toxins investigated in high quality studies. It remains to be seen if the same positive response can be duplicated with the use of other major FDA approved botulinum type A toxins such as Xeomin, Dysport and Diddify or with the type B toxin, Myobloc.

Cardiology: Treatment of Atrial Fibrillation (Irregular Heart Beats)

The human heart is a marvel of function and engineering. It has four chambers; two small ones called atriums with thin walls, and two large ones called ventricles with thick walls. The two atriums (atria) are located above the ventricles and each atrium has an opening into the ventricle below, on the same side. There are valves between atria and ventricles which control the blood flow through them. The mitral valve is located on the left and the aortic valve is located on the right side (Fig. 19.4).

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

In recent years, the importance of GP as an extensive combinations of nerve cells and fibers has been emphasized with some authors describing it as a “little brain sitting over the heart” (Fig. 19.5).

Five locations for ganglionic plexi (GP) containing sympathetic and parasympathetic cells and fibers have been identified around left and right atria embedded in the small fat pads. These overlie the surface of the right atrium, superior surface of the left atrium, posterior surface of the right atrium, posterior medial surface of the left atrium and inferiolateral aspects of the posterior left atrium. Abnormal electrical activity in these sites which are often located close to the pulmonary veins, can cause a condition called atrial fibrillation.

Atrial fibrillation (AF) affects 2.5% of the general population (9% or higher after age 75) and is associated with an annual stroke incidence of 5% [16]. About 1 out of 4 adults develop atrial fibrillation during their life time [17]. With increase in our aging population, the incidence and prevalence of atrial fibrillation is on the rise (17.8% after age 85), imposing a growing cost on the health care budget [18].

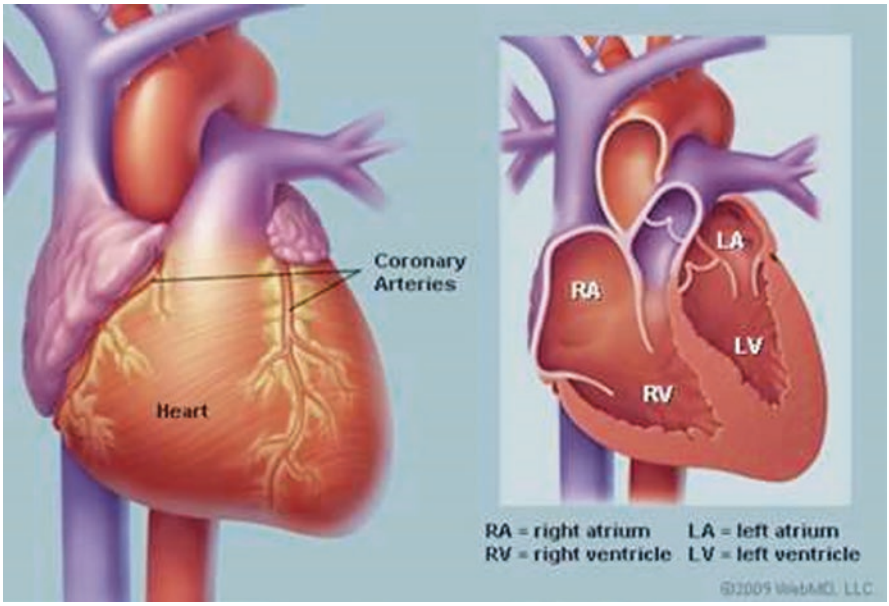

Fig. 19.4 Right: chambers of the heart and large blood vessels. Left: coronary arteries that feed the heart muscle. (Courtesy of Dr. Poonan Sachdev and WebMD editorial contributors)

Atrial fibrillation is characterized by irregular, fast and somewhat chaotic beating of the upper two chambers (atria) of the heart. Several factors can cause atrial fibrillation; most notable among them are high blood pressure, damage to the heart structure from coronary artery disease (vessels that feed the heart muscle), myocardial infarction (heart attack), abnormal thyroid function, diabetes, kidney disease and a congenital heart anomaly. Atrial fibrillation is a frequent complication of Coronary Artery Bypass Grafting (CABG) surgery that replenishes blood supply to parts of the heart that lack sufficient blood supply. Experimentally, researchers have produced atrial fibrillation in animals by electrical stimulation of the vagus nerve which supplies parasympathetic innervation to the heart (the nerve that slows the heart beat).

The symptoms of AF include shortness of breath, palpitation (rapid heartbeat) and fatigue. However, AF can be asymptomatic and may suddenly present itself with a stroke (due to the travel of a small blood clot to the brain). Beta-blocker medications, calcium channel blocking agents, digoxin and drugs that thin the blood (anticoagulants) are commonly used in patients with AF for normalization of the heart rate and prevention of stroke. Currently used medications for control of atrial fibrillation are effective but often require careful titration. Side effects of these medications are not infrequent including bleeding that can be sometimes serious) as a side effect of anticoagulants. Severe and recalcitrant cases of AF may respond to ablation of the AV node by high energy radio frequency pulse. Ablation of the atrioventricular (AV) node helps a large number of patients with AF, but the procedure requires insertion of a permanent heart pacemaker.

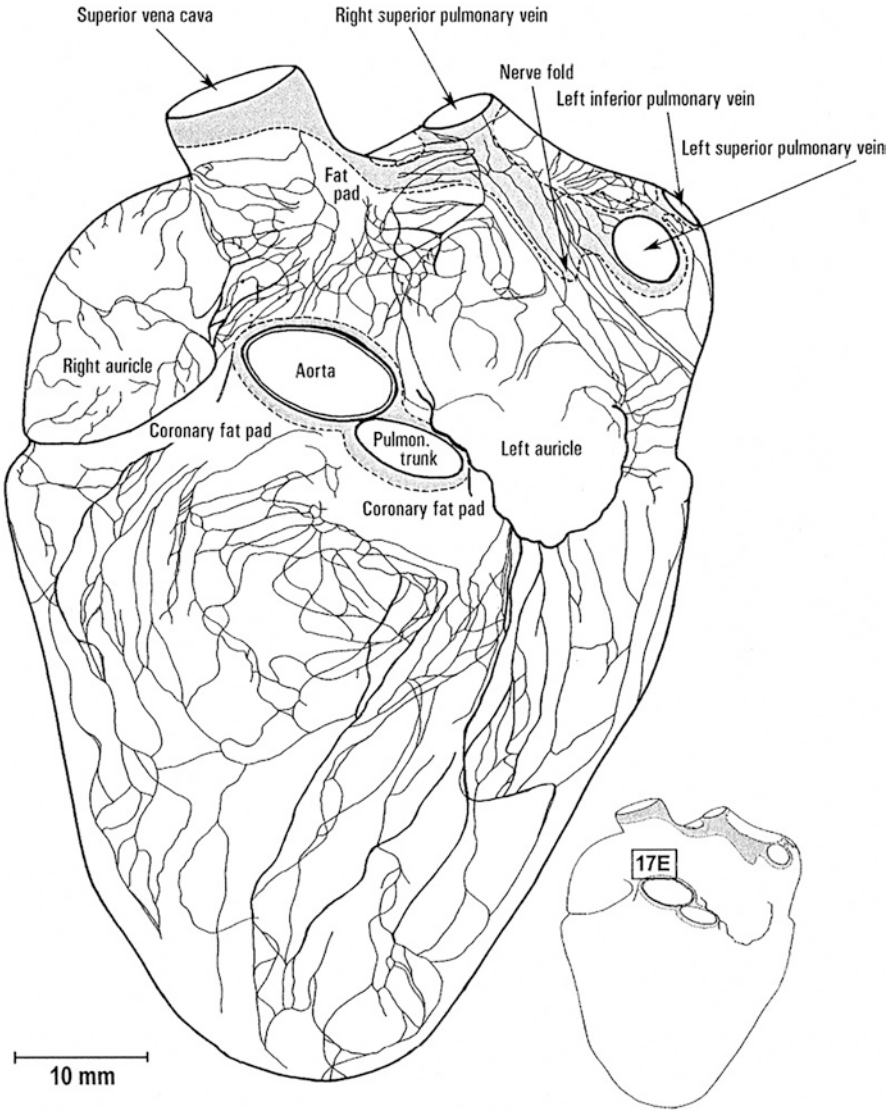

Fig. 19.5 Ganglionic plexus of the heart with nerve cells innervating the heart located in fat pads close to large vessels of the heart and diffuse nerve fibers that excites the heart. (From Pauza et al. [15]. Courtesy of the publisher, Wiley and Sons)

Since injection of botulinum toxins inhibits the activity of acetylecholine (see previous chapters), the chemical that is the neurotransmitter for parasympathetic nerve (vagus nerve), researchers began to explore the potential role of botulinum toxin therapy in atrial fibrillation. It has been shown that injection of botulinum

toxin A (Botox) into the ganglionic plexus (GP) of dog's heart can suppress AF caused by electrical stimulation of the dog's vagus nerve [19]. Similar results were found in electrical stimulation induced atrial fibrillation of sheep following injection of Botox (25 units) units into different surface fat pads (containing GP) of the sheep's heart [20].

Pukoshalov and coworkers [21] first investigated the effect of botulinum toxin injections into the GP of human heart in a double- blind, placebo-controlled study. Prior to cardiac bypass surgery, 60 surgery candidates were randomized into toxin and saline groups (30 each). After opening the chest wall (thoracotomy), 50 units of Xeomin or 1 cc of normal saline (placebo) was injected into each of four pericardial fat pads containing GP. During the first 30 days after surgery, 2 of 30 patients (7%) in the botulinum toxin group and 9 of 30 patients (30%) in the placebo group experienced recurrence of atrial fibrillation (statistically significant difference, $P = 0.024$). Over the next 12 months, none of the patients in the Xeomin group experienced recurrence of AF, while 7 of the 30 (27%) subjects in the placebo group had recurrences (also statistically significant, $P = 0.002$). No patient reported any side effects. Xeomin is a Botulinum toxin type A like Botox, with units comparable to Botox.

In another study published 4 years later in 2019, a group of investigators assessed the effect of injection of 50 units of Xeomin into each 4 GPs around the heart of 60 patients with AF and compared the results with placebo injection (saline) at 36 months postinjection [22]. The results showed that while in the saline injected group, 50% still had AF, in the BoNT injected group only 23.3% still had AF at 36 months post injection. The number of hospitalizations was also reduced in the toxin injected group compared to saline injected group (2 patients versus 10 patients). In another study, fewer patients with Botox injections (50 units into each GP) prior to cardiac surgery developed AF after cardiac surgery compared to those who had received placebo injections (36.5% versus 47.8%), but the difference was not statistically significant [23]. The latter study, however, also included patients who underwent valve replacement surgery, whereas the surgery in the first two studies was coronary artery bypass grafting (CABG). In all three studies, side effects after BoNT injection were comparable with the side effects in the placebo group who were injected with saline; all side effects were defined as insignificant. These studies strongly suggest that for recalcitrant AF caused by CABG surgery, BoNT injection into GP would be a good alternative to AV node ablation; BoNT injection, unlike AV node ablation, does not require the patient to be placed on permanent pacemaker. Nevertheless, there is a need for further well-designed studies to carefully investigate the efficacy of preventive value of BoNT injection into heart's fat pads in patients undergoing cardiac surgery. These studies should control for potential confounding factors such as type of surgery, left atrial size, dose and site of injection of botulinum toxin as well as other relevant factors [24].

Cancer Associated Disorders

Cancer–Related Pain

Over the past 25 years, it has been shown that injection of botulinum toxins (A or B) into muscle or skin can relieve pain. This is due to the fact that Botox and other toxins deactivate the function of pain transmitters (glutamate, substance P, others) both in the peripheral nerves and in the central nervous system [25–27]. The palliative role of BoNTs in a large number of pain disorders [28–32] has been discussed in detail in Chap. 6 of this book.

Cancer can cause pain through several different mechanisms. The most commonly reported and best-studied type of pain associated with cancer is the pain felt at the site of surgery and radiation in patients with head and neck cancer (throat, tonsils, etc.). This form of pain can be severe and disabling and may significantly impair the quality of life as noted in the case described below from the author's experience.

Patient Example

A 48- year-old man had bilateral surgery on the neck (neck dissection), followed by neck radiation and chemotherapy for cancer of the larynx (beginning of the wind pipe in the throat). Two years later, he developed severe pain in the left side of the neck and painful spasms of the shoulder muscle (trapezius) close to the neck. The pain was present almost every day and impaired his quality of life significantly. Treatment with pain killers including potent agents (opioids and fentanyl), at best, provided modest relief. He was referred by his physician to the Yale Botulinum Toxin Clinic for management of his neck pain. Injection of the anterior neck region on the left, in the areas of scar and keloid formation, and left shoulder muscle with Botox resulted in marked reduction of pain and improvement of the patient's quality of life. The dose for the neck injection was 10–20 units/site (Fig. 19.6, areas marked by x) and for the shoulder it was 30–40 units/site. Over a follow- up period of 3 years, patient received injections every 4–5 months and, each time, reported satisfaction. There were no side effects.

During the years 2005–2015, the author of this chapter and his colleagues at Yale University studied the effect of botulinum toxin therapy in cancer related pain. The results were published in two small clinical trials, one on 7 and the other on 12 patients [33, 34]. In these studies, the investigators used Botox or Xeomin (another botulinum toxin type A with units comparable to Botox) to relieve neck pain in patients with history of surgery and/or radiation for laryngeal, throat or tongue cancer. A total of 80–120 units of Botox or Xeomin was injected into painful scars and indurated keloids and, sometimes additionally, into the adjacent painful muscles of the neck in order to relieve the chronic pain (Fig. 19.6). The patients' level of pain

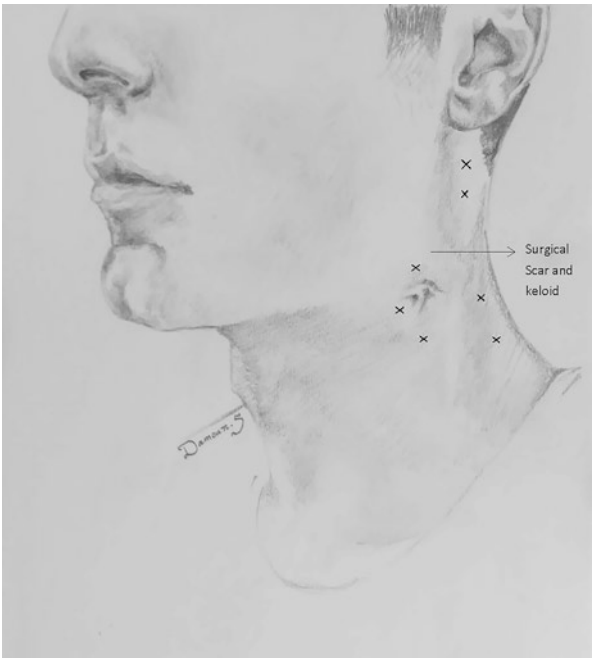

Fig. 19.6 Sites of Botox injection in a patient with persistent neck and shoulder pain after surgery and radiation for throat cancer. (Drawing courtesy of Dr. Damoun Safarpour. From Mittal and Jabbari [43]. Courtesy of Toxins. https://creativecommons.org/licenses/by/4.0/)

and quality of life was assessed at baseline, and after injection every 4 weeks for 3 months. In 80% of the patients, local injection of Botox or Xeomin resulted in marked reduction of local pain. Approximately half of the patients reported significant improvement of their quality of life. In recent years, several authors also reported improvement of cancer associated pain following local botulinum toxin injections in small series of patients [35–42].

Pain Due to Metastasis by Cancer

Patient Example

A 62- year old female, an intelligent and accomplished writer with history of lung cancer, experienced severe jaw pain and stiffness of the jaw muscles that gradually locked her jaw and prevented her from eating solid food. An MRI of the head showed an enlarged right masseter muscle (the masseter muscle raises the lower jaw and closes the mouth- Fig. 19.7) presumably due to metastatic cancer.

Pain killers and muscle relaxants offered little help. The jaw gradually locked and prevented her from eating solid food. She lost 15 pounds of weight over 3 months and suffered from severe depression. Patient also complained of severe jaw pain that she rated as 8 on a scale of 0–10.

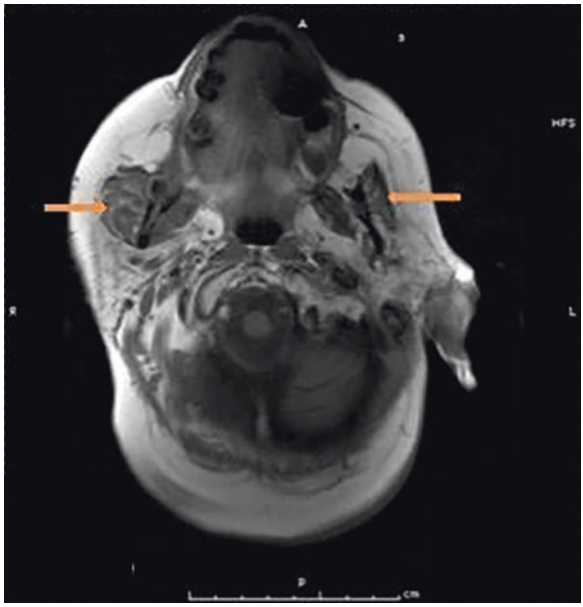

Fig. 19.7 MRI showing an enlarged masseter muscle on the right side of the image (right masseter) due to invasion by tumor tissue. (From Safarpour and Jabbari 2023. Courtesy of toxins https://creativecommons.org/licenses/by/4.0/)

Under an approved hospital protocol and with patient's consent, Botox was injected into the masseter muscles (overlying the jaw), 70 units on the right and 30 units on the left side. Within 3–4 days after Botox injection, the contracted masseter muscles relaxed, and the jaw was unlocked allowing the patient to eat solid food. She also reported significant reduction of her jaw pain within days following the Botox injections. The effect of botulinum toxin injections lasted for 2–3 months. She experienced no side effects following injections into the masseter muscles. Repeated Botox treatment every 2–3 months had the same effect and made the patient comfortable during the last 18 months of her life.

Neuropathic Pain Caused by Chemotherapy for Cancer

Immune modifying drugs or drugs that are used for chemotherapy of cancer are toxic and often cause systemic complications. Peripheral neuropathy is common among these side effects. This form of damage to the peripheral nerves is painful and involves mainly the distal part of the limbs with the symptoms presenting most notably in the feet.

The pain is a neuropathic type of pain characterized by its sharp nature and burning quality. It can be constant and can disturb sleep. The author of this chapter observed that injection of Botox into or under the skin at multiple sites with a thin needle (gauge 30) may relieve pain in patients with this type of neuropathy. Botox injections themselves are painful in these patients since their skin is sensitive, but

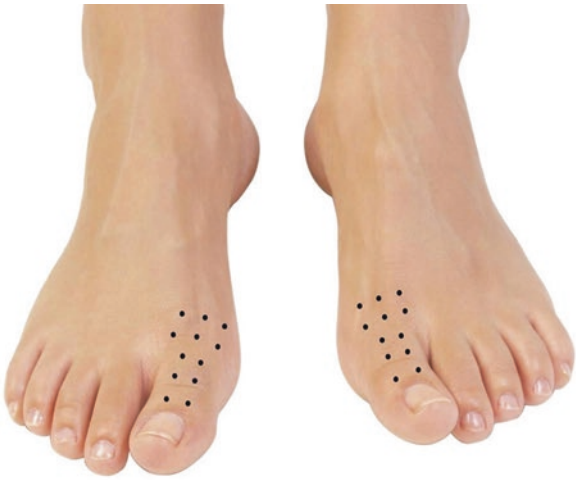

Fig. 19.8 The sites of Botox injections in the patient with cancer and neuropathic pain caused by immune modifying drugs. (From author's personal collection)

the subsequent pain relief that lasts for months makes it acceptable to most patients. Before the injections, the skin can be numbed by Emla cream and, additionally, by anesthetic spray.

Patient Example

A 64- year-old man complained of severe burning pain involving the top of his feet (mainly in the front and above the big toes) during treatment with immune modifying agents tacrolimus and cellcept which were prescribed for management of cancer of the bone morrow. He had been diagnosed with a myeloclastic syndrome (a form of bone morrow cancer) a year earlier. The pain was described as sharp, burning and unbearable at night. The most painful areas were above the big toes, on the dorsal aspect of the feet. Pain killers provided no relief. A week after injection of Botox into 10–12 sites of each affected foot (Fig. 19.8), the patient reported significant pain relief that lasted for months. The Botox dose was 1.5–2 units/site.

Botulinum Toxin Injections Help Complications That Follow Esophageal Cancer Surgery

Removal of esophageal cancer can cause significant narrowing (stricture) of esophagus impairing the passage of food. Wen and coworker [44], in a double- blind, placebo-controlled study, have shown that injection of Botox into the esophagus before tumor resection can significantly reduce development of post-surgical stricture (Botox: 6.1% versus placebo 32.4%, statistically significant P = 0.02). Another

complication after esophageal cancer surgery is development of gastroparesis (weakness of stomach muscles) which leads to a delay in passage of food from stomach into the gut for absorption. Investigators have shown that injection of botulinum toxins (Botox and others) into pylorus (the circular muscle ring between stomach and first part of the gut) by relaxing this muscle ring (sphincter) and promote passage of the food into the gut [45–47].

Botulinum toxin injections are shown to be helpful in preventing or resolving complication that arise from parotid gland surgery. Parotid glands are located under the skin at the region of the jaw close to masseter muscles (muscles used for chewing). They secrete saliva. After removal of cancerous parotid glands a fistula or cyst (sialocele may develop at the site of surgery. Investigators have shown that injection of botulinum toxins into the parotid glands prevents development of fistula or cyst in a substantial number of patients [48, 49]. This function is accomplished through drying the saliva via inhibiting release of acetylcholine, the nerve transmitter that excites the parotid glands.

Another complication of parotid surgery for cancer is development of unpleasant and excessive facial sweating while chewing food (gustatory hyperhidrosis). Since the nerve transmitter for sweat glands is also acetylcholine, injection of Botox with a small and thin needle over the sweating region (multiple injections) can dry the skin for several months. The effectiveness of Botox injections for treatment of gustatory hyperhidrosis after parotidectomy has been reported in several publications [50, 51].

Dermatology

Psoriasis

Psoraias is a chronic skin disease characterized by red plaques (plaque psoriasis) covered by silvery scales that can affect any part of the body (skin, nail, scalp). Psoriasis is an autoimmune disease causing skin lesions through inflammation. It affects 3% of the adult US population and 0.1% of US children [52]. Intense itch associated with psoriatic skin lesions impairs the patients' quality of life. Most affected patients have plaque psoriasis (raised plaques as described above); additionally, approximately 30% have inverse psoriasis where the lesions are in body folds (axilla, groin, genitals) and usually have no scales. As psoriasis is a systemic inflammatory disease; patients with severe psoriasis are prone to develop cardiovascular complications and diabetes.

Treatment of psoriasis is aimed at alleviation of patients' symptoms and healing the lesions as well as controlling the basic immunological problem in order to prevent development of new lesions and spread of the disease. The first line of treatment is using phototherapy (exposure to ultraviolet light) and application of topical creams such as those containing steroids to heal skin lesions. Careful removal of the

scales also promotes healing. In case of severe psoriasis involving large parts of the body, use of drugs that strengthen immunity and reduce inflammation are recommended. In the past 10 years, several of these drugs have been approved by FDA for use in the US. For example, Skyrizi (Risankizumab) selectively binds to the inflammatory agent interleukin 23 and prevents its action. These drugs are not however, free of serious side effects and should be used under supervision of specialized physicians. Since the treatment of milder forms of plaque or inverse psoriasis by phototherapy and steroid creams is not always successful, a search for new modes of therapy continues in the field of dermatology.

Botulinum Toxin Treatment

After noting that local injection of botulinum toxins decreases local inflammation in animal models [53], investigators began to explore the effectiveness of local injections of botulinum toxins in improvement of psoriatic skin lesions. In 2008, Zanchi and co-workers [54] treated 15 patients with plaque or inverse psoriasis (psoriasis affecting folded areas like axilla) with botulinum toxin injections. Botox, 50–100 units, was injected into multiple areas of the lesions. After 12 weeks, all patients reported improvement of itch (using VAS score) and. in 87% of the patients' skin lesions (redness and induration) improved. This observation was seconded by several others over publications in the past 15 years (Table 19.2).

The mostly positive data from these studies are supported by several case reports graphically demonstrating the healing of psoriasis lesions after Botox injection (Fig. 19.9).

The negative conclusion of Todberg's study (Table 19.2) is at odds with the rest of the reports in the above table that have found botulinum toxin injections useful in treatment of psoriasis. However, the toxin dose in the Todberg study (using Dysport) was much smaller than the dose used in the above described Botox studies (each Botox unit is equal to 2.5–3 Dysport units). Since success in botulinum toxin therapy is highly dependent on the applied dose, the conclusion expressed in the Todberg's study has to be considered with caution.

Recalcitrant Itch

Itch is a common human complaint, experienced often by patients affected by different skin disorders. Recalcitrant itch is a major physical and psychological nuisance and impairs patients' quality of life. Certain chemicals seem to be involved in sustenance of itch such as histamine and calicitonin gene related peptide (CGRP). The latter is a well-known pain transmitter which is inhibited by botulinum toxin injection. Sensation of itch is believed to be transmitted to the brain through the very same thin sensory nerve fibers (C fibers) that convey neuropathic pain (sharp,

Table 19.2 Reports of botulinum toxin efficacy in treatment of psoriasis

Author and date	#pts., Study type	Type of psoriasis	Type of toxin and total dose (units)	Assessment methods, clinical features	Results
Zanchi et al. [54]	15, OL	Plaque and inverse	Botox, 50–100	VAS for itch, redness; color assessed by observation	At 12 weeks, itch improved in 87%; redness and duration improved in all patients
Saber et al. [55]	1, OL	Inverse, affecting axilla	Botox, 100	Redness and color assessed by observation	At 4 weeks, extensive skin lesions were reduced to small areas of pale redness
Gilbert et al. [56]	1	Inverse, single plaque	Dysport, 30	Redness, induration	Improvement noted at 3 weeks. Total healing over succeeding weeks
Todberg et al. [57]	8, Db-PC	Plaque psoriasis	Dysport, 36	Clinical assessment of redness and induration	No patient showed improvement of lesions
Botsali et al. [58]	2, OL	Nail psoriasis	Dysport, 30	Nail improvement and clearing	Significant improvement 4 months post-injection
Gonzalez et al. [59]	8, OL	Plaque psoriasis	Dysport, 50	Redness, infiltration	Significant improvement of redness and infiltration, 2 patients reported significant improvement in itch
Khattab and Samir [60]	35, NSP	Plaque psoriasis	Refinex (Chinese toxin) 100	Redness, induration TSI	85% of the patients showed improvement of TSI with improvement of redness and induration

TSI psoriasis severity index, *OL* open label, *Db-PC* double blind, placebo controlled, *NS* blinding not specified (toxin injection was compared with fluorocil injection)

burning) [61]. Treatment of recalcitrant itch includes use of drugs that inhibit the function of histamine (antihistaminic drugs), as well as drugs that are used for treatment of neuropathic pain such as gabapentin. Unfortunately, in many patients results do not meet patients' satisfaction.

Animal studies and studies on human volunteers have shown that local injection of botulinum toxin can inhibit the function of CGRP and histamine [62, 63]. These observations encouraged researchers to look at the effect of botulinum toxin injections into recalcitrant itchy skin lesions. They found that intense itch associated with different skin lesions improves with injection of botulinum toxin into the affected area (Table 19.3).

The data in the Table 19.3 show that although high quality studies are not yet available for this indication, botulinum toxin injection has a significant potential to suppress recalcitrant itch caused by different disorders.

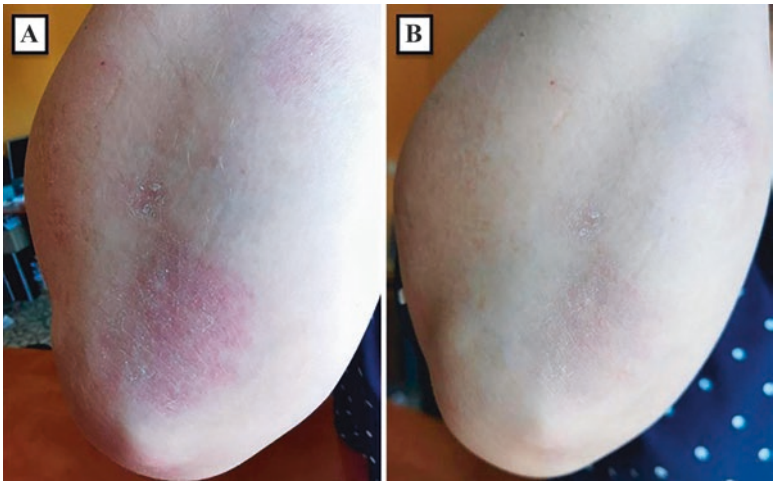

Fig. 19.9 (**a**) Psoriasis of the elbow and extensor surface of the forearm a month before Botulinum toxin injection (**b**) significant improvement of psoriatic lesion following injection of 1000 units of Dysport (approximately 300–350 units of Botox) for treatment of elbow spasticity (see Chaps. 6 and 7 for spasticity treatment in stroke and multiple sclerosis with botulinum toxins). (Courtesy of Dr. Popescu and colleagues 2022. Reproduced under Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/))

Raynaud's Syndrome (RS)

Described by Maurice Raynaud in 1862 (part of his thesis), this is a disabling clinical condition characterized by poor circulation of the digits causing significant skin changes (blue or red discoloration) and pain in the hand and fingers. The condition worsens after exposure to cold and emotional stress [73]. In severe cases, poor circulation may cause intolerable pain associated with gangrene of the fingers. Raynaud's syndrome (RS) is classified into primary and secondary types [74]. In primary RS, the cause is unknown. Secondary RS is usually associated with diseases caused by failure of immune system such as scleroderma and cancer. Excessive smoking and excessive use of certain drugs (especially anti-cancer drugs) are also major contributing factors. Several modes of treatment have been tried in RS with limited success. Among drugs, gabapentin and serotonin uptake inhibitors offer analgesic effect. Laser therapy and acupuncture are also partially effective.

The reason for considering botulinum toxin therapy for alleviating the symptoms of RS is based on two premises: (1) vascular tone in the fingers is maintained by the sympathetic nervous system using acetylecholine as nerve transmitter. Botox and similar toxins are known to inhibit the release of acetylcholine from nerve endings (see Chap. 2 of this book). (2) Botulinum toxin injections into muscle and skin can alleviate pain due to inhibition of known pain transmitters [75]. The data from clinical trials and on this subject are presented in Table 19.4. Single case reports are not included in this table.

Table 19.3 Reports of itch responding to local injection of botulinum toxins into the affected region

Author and date	# pts.	Associated disease	Itch location	Toxin type and total dose in units	Method of assessment	Results
Heckmann et al. [64]	4	Lichen simplex, 5 skin lesions	Two spots, lower limbs	Dysport, 20–80	VAS for itch 0–10 scale	Itch subsided in 3–7 days. Skin lesions cleared in 2–4 weeks
Zanchi et al. [54]	15	Psoriasis	Different places: Armpits, groin,	Botox, 50–100	VAS for itch 0–10 scale	Itch improved in 87% of the patients
Salardini et al. [65]	1	Post-surgical scar	Right frontal region	Botox, 15	Patient report	"Marked reduction of itch in a few days"
Kavanagh and Tidman [66]	1	Notalgia paresthetica[a]	Posterior aspect of the arms	Botox, 100,	Patient report	Marked reduction of itch for months reproduced with repeat injections
Akhter and Brooks [67]	9	Burns	Different parts of the body	Botox, dose not specified	VAS for itch 0–10 scale	Itch intensity of 8–10 dropped to 0–4. Most patients to 0
Gonzalez et al. [59]	8	Psoriasis	Not specified	Dysport, 50	Patient report	Significant improvement of itch in two patients
Datta et al. [68]	1	Notalgia paresthetica	Not specified	Botox dose not specified	Not specified	Marked reduction of itch
Gharib et al. [69]	32	Burn scar, shingles, psoriasis,other skin lesions	Different parts of body	Botox, 50–100	VAS for itch 0–10 scale	Statistically significant decrease in intensity in all patients
Klager et al. [70]	1	Fox-Fordyce[b] disease	Right armpit	Botox, 50	VAS for itch, 0–10 scale	Initial itch:10 Itch level dropped to 3 after Botox injection
Alam et al. [71]	9	Post-surgical scar region	Face cancer	Type E toxin, 2.5 nanogram	VAS for itch 0–10 scale, scar scale	At days 2 and 8 post- surgery no patient in toxin group had itch compared to 75% and 50% in the placebo group
Mineroff et al. [72]	1	Shingles	Left upper neck	Botox, 50	Patient report	Marked reduction of itch for 3 months

VAS visual analogue scale

[a]Notalgiaparesthetica: chronic itch over the lower part of shoulder blade more common in elderly female

[b]Fox-Fordyse disease: a medical condition characterized by pathological changes in the sweat glands and chronic itch

A review and meta-analysis of data published in 2023 concluded that the reported data in the literature (Table 19.4) support the efficacy of botulinum toxin treatment to reduce the symptoms of RS [89]. However, this conclusion was challenged by a very recent double-blind, placebo-controlled study that did not find any difference between placebo and Botox in improving the symptoms of RS [90]. Yin and coworkers [91] stated that the negative results of that study [90] could be due to several factors such as longer duration of the disease in the Botox group, poor training of patients to report RP episodes, ignoring skin color changes and not reporting ethnicity of the patients which could influence the results. More high quality studies are necessary to support or refute the effectiveness of botulinum toxin treatment in Raynuad's syndrome.

Teeth Grinding (Bruxism)

Teeth grinding is a common medical problem that can affect children and adults and may present during wakefulness or sleep. It affects up to 31% of adults [92]. Severe teeth grinding can destroy teeth, cause jaw pain and headaches. Teeth grinding during sleep interrupts sleep of both patient and the bed partner. Medications like clonazepam (clonopin) provide modest relief, but may cause significant daytime sedation. Several high quality studies (double- blind and placebo- controlled), though small in number, have demonstrated that injection of Botox into the temporalis and masseter muscles (Fig. 19.10) can improve teeth grinding. These two muscles close the jaw.

A placebo-controlled study published in 2018 assessed 23 patients with teeth grinding during sleep and compared the outcome in 13 patients assigned randomly to Botox with 10 patients assigned to the placebo group (blinded study) [93]. Botox was injected into temporalis muscles (40 units on each side) and masseter muscles (60 units on each side). Authors concluded that injection of Botox into those muscles safely improves teeth grinding during sleep with no significant side effects. Two patients reported transient cosmetic change in their smile.

Two more recent blinded and placebo-controlled studies [94, 95], one investigating a larger number of patients [93] with bruxism compared the effect of Botox treatment with placebo. These studies provided results similar to the two abovementioned studies and came to a similar conclusion. One of the two [95] found that injecting even small units of Botox into the masseter muscle only (10 units) can improve pain and discomfort associated with night time teeth grinding. These encouraging data indicate that Botox injections into muscles of mastication can improve teeth grinding during sleep and wakefulness without causing major or persistent side effects.

Table 19.4 Botulinum toxin effect on the symptoms of Raynaud's Syndrome

Author and date	Type of study	#pts	Toxin type and total dose in units	Method(s) of assessment	Results
Uppal et al. [76]	Pros	20	Botox, 100	Pain (VAS), skin color change, disability (dash score)	Reduction pain, color and disability in 85%, 75%, and 85% of the patients, respectively
Fregene et al. [77]	Retro	26	Botox, average 77	Pain (VAS), digit oxygen, healing finger ulcers	Pain, digital oxygen saturation and finger ulcers improved in 75%, 57% and 48% of the patients, respectively
Neumeister et al. [78]	Retro	33	Botox 40/hand; 4 injections	Pain(VAS), healing of ulcers	Reduction of pain: 86%; healing of ulcers: All patients
Goldbeg et al. [79]	Retro	20	Botox, 10–20/ finger	Pain(VAS), disability (dash score),	Pain: In 86% of pts.; dash score for disability: Reduced over 14 points at 6 weeks; clinical success in 84% of pts
Shanavandeh et al. [80]	Pros	26	Botox, 20 injected at the base of each involved finger	Healing of ulcer, pain(VAS), local small bleeds	Healing of ulcers: 95%; pain: Improved in all; reduced number of small bleeds
Medina et al. [81]	Retro, 3 years follow up	15	Botox, 4–8 injected into the base and lateral aspect of all fingers	Pain (VAS). Weekly episodes of RP, finger ulcers	At week 8 post injection: Pain and RP episodes markedly reduced, ulcers healed in 5 of 7 patients
Motegi et al. [82]	Pros, blinded, dose comparison	45	Myobloc 3 groups, 250, 1000 and 2000	Number of ulcers, skin temperature, RP score and pain (VAS_)	At week 4 after injection: All outcomes significantly improved in 1000 and 2000 dose groups
Bello et al. [83]	DB-PC, all had scleroderma	40	Botox, 5–10 into 7 hand areas	Blood flow to the hands, VAS for pain, RP episodes	No significant difference between groups. At 4 weeks VAS score was lower in Botox group
Quintana-castanedo et al. [84]	Pros	8	Botox. 36/ hand, base of all fingers, 7 injections	Pain (VAS), RP episodes	At 4 weeks post-injection: 6 patients had no pain;6 had significant reduction of RP episodes
Dhaliwal et al. [85]	Pros	40	Botox, 100	Pain(VAS), hand swelling, change in color	All parameters markedly improved in 48% of the patients

(continued)

Table 19.4 (continued)

Author and date	Type of study	#pts	Toxin type and total dose in units	Method(s) of assessment	Results
Du et al. [86]	Pros,	32	Botox 10 vs no Botox, injected into 2+3rd and 3rd and 4th fingers	Pain(VAS), RP episodes, microscopic parameters	VAS: No improvement; RP episodes significantly lessened, microscopic parameters improved
Seyed-mardani et al. [87]	Pors	11	Botulinum toxin A 50/hand	Raynaud score, skin color, pain(VAS)	All significantly improved at two months
Motegi et al. [88]	Pros	10	Botox, 10/hand	Pain: Measured by VAS, RP frequency and intensity	Both pain and RP frequency/intensity improved after Botox injection

DB-PC double blind placebo controlled, *Pros* prospective, *Retro* retrospective, *VAS* visual analogue scale for pain (0–10), *RP* Raynaud phenomenon episodes, Myobloc is a type B toxin (Botox is type A)

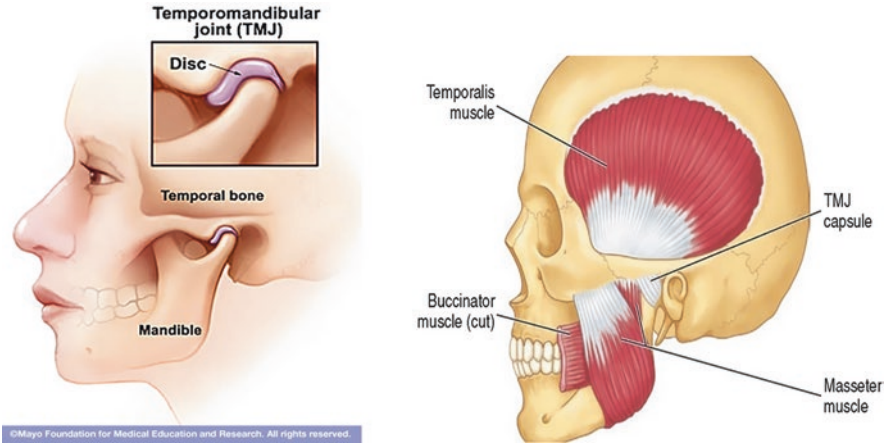

Fig. 19.10 Temporalis and masseter muscles. (Printed with permission from Mayo Foundation)

Rectal Pain Associated with Hemorrhoidectomy

Local muscle pain along the line of excision, after hemorrhoidectomy, is a common complaint. In some patients, the pain can be severe and disabling and may persist for months despite use of potent analgesics. Over the past 20 years, researchers have explored the effectiveness of botulinum toxin injections into the anal sphincter (the circular muscle that opens and closes the anus) before, during and after hemorrhoidectomy in order to prevent post-hemorrhoidectomy pain.

Davies and coworkers conducted a careful, double- blind (both physician and patient blinded to the type of injection) study of 50 patients who had undergone hemorrhoidectomy [96]. Injection of 20 units of Botox into the anal sphincter prior to removal of the hemorrhoids, markedly reduced postsurgical painful spasms of the anal sphincter, an effect which was statistically significant compared to placebo (saline) injection. The peak pain relief was at the sixth or seventh day after surgery. In another high quality study (blinded and compared with placebo), Dr. Alavandipour and her colleagues [97] have shown that injection of Botox during surgery into the anal sphincter significantly reduced pain after surgery compared to placebo injection as assessed at 12 and 48 h, as well as 7 and 14 days after operation. In addition, in the Botox injected group, the post-operative wound healed much faster than the group that had placebo (salt water) injection. Two other high quality investigations published in 2020 and 2022 [98, 99] also found similar results by injecting Botox shortly after surgery. A comparative study of Botox with local application of glycerine nitrate found botulinum toxin injections more effective than glycerine nitrate for relief of post-surgical pain [100].

The Role of Botulinum Toxin Injections in Complex Midline Abdominal Hernia Repair

The abdominal wall muscles consist of two major components: the front muscles of abdominal wall engulfing the belly button (called rectus abdominalis) and oblique lateral muscles. The existing tone in lateral abdominal oblique muscles tends to pull the anterior wall muscles laterally and to the side. This causes a problem after the repair of a large midline abdominal hernia since the pulling power of lateral oblique muscles delays healing after hernia repair surgery. Several studies have shown that relaxing lateral abdominal oblique muscles by Botox injections prior to surgery can expedite healing of the abdominal wall after hernia repair surgery [101–103].

Conclusion

Emerging literature shows potential new indications for botulinum toxin therapy in several medical conditions: depression, atrial fibrillation, cancer related pain, post-surgical pain (hemorrhoidectomy, hernia repair), teeth grinding (bruxism), psoriasis, recalcitrant itch, jaw pain in temporomandibular disorder and in Raynaud's syndrome.

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