Chapter 17
Botulinum Toxin Therapy-Future Perspectives

Introduction

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

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

Psychiatry – Depression

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

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

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

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

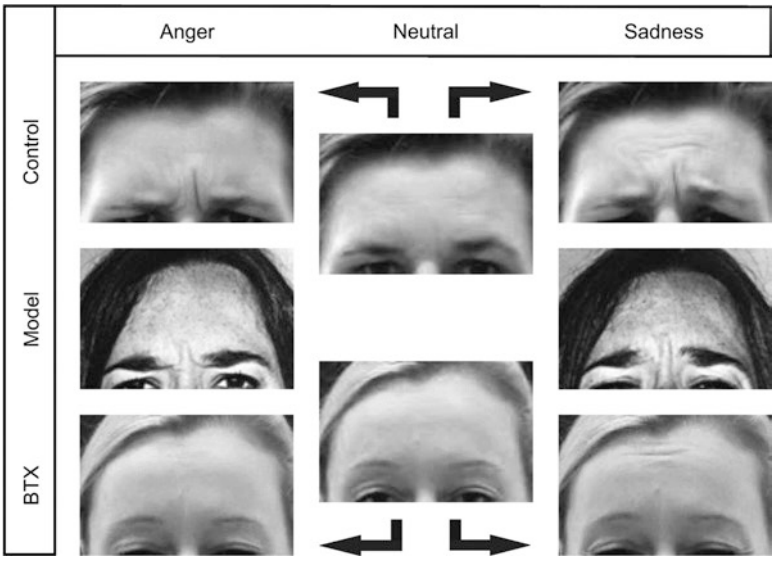

Fig. 17.1 The function of glabellar muscles-frowning during volition (not shown) and during anger and sadness. Lower part of the figure shows the effect of Botox treatment. From Hennenlotter and co-workers 2009- Journal Cerebral Cortex with permission from Oxford Academic Press

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

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

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

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

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

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

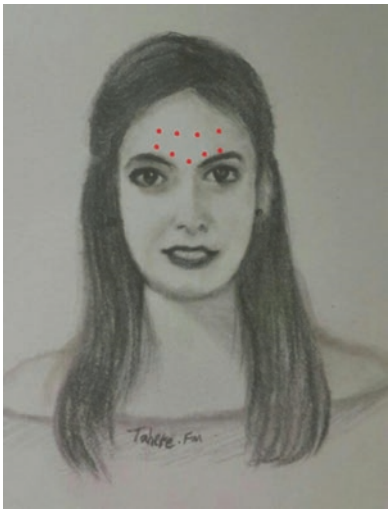

Fig. 17.2 Commonly used areas of Botox injections for glabellar lines (*lower row*) and forehead wrinkles (*upper row*). Drawing, courtesy of Dr. Tahere Mousavi

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

Cardiology (Irregular Heart Beats –Atrial Fibrillation)

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

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

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

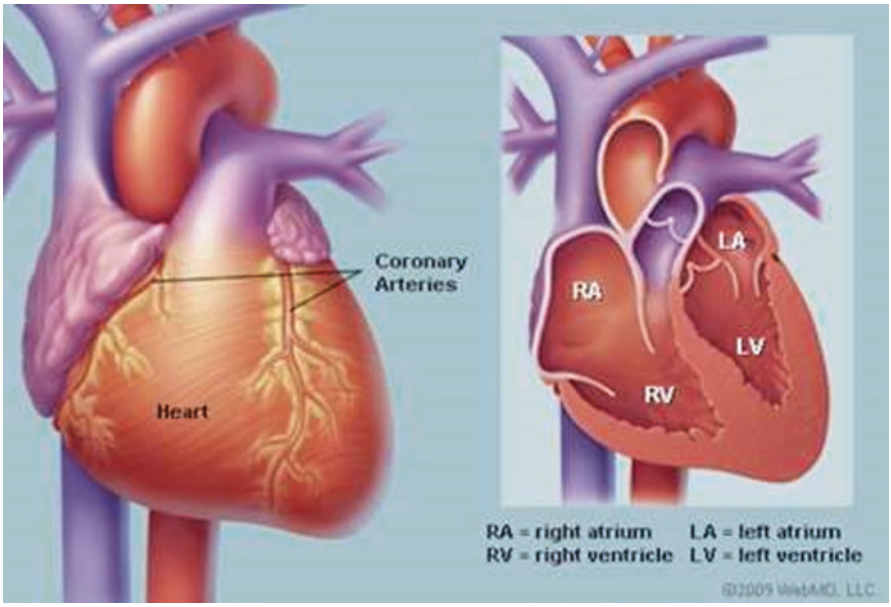

Fig. 17.3 (**a**) right: chambers of the heart and large blood vessels. (**b**) right: coronary arteries that feed the heart muscle. Printed with permission form WebMD

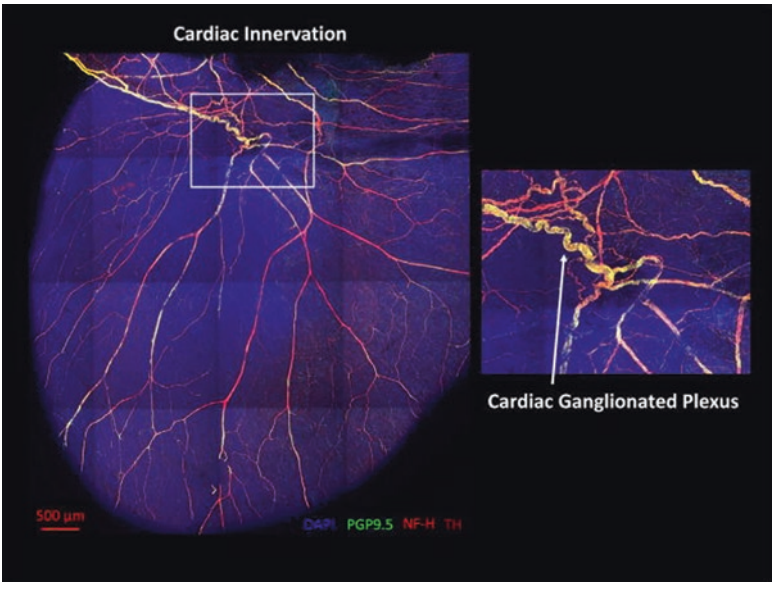

Fig. 17.4 A ganglionic plexus (nerve cell and fiber) and extensive network of nerve fibers that innervate the heart. From Buckley and co-workers in the journal of Heart Rhythm 2017. Printed with permission from publisher

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

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

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

Pain Medicine

Cancer–Related Pain

Cancer can cause pain through different mechanisms:

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

Patient Example

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

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

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

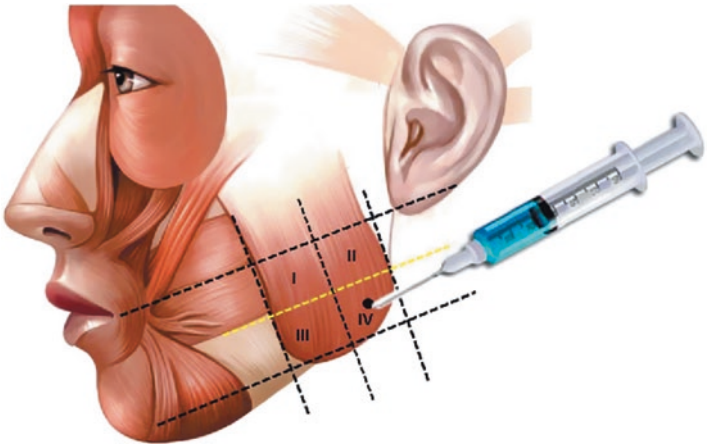

Fig. 17.5 The location of masseter muscle and how Botox injection the into the masseter is often performed. In this example 4 sites are injected. Some injectors including the author prefer two sites. From Wei and co-workers 2015. Reproduced with permission from publisher, Wolters-Kluver

Patient Example

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

c) Neuropathic Pain caused by Chemotherapy for Cancer.

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

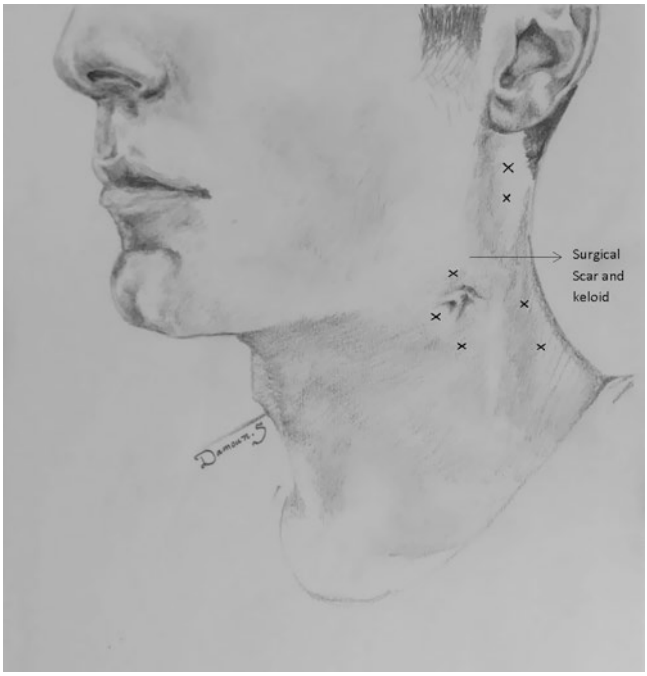

Fig. 17.6 Sites of Botox injection in the case with persistent neck and shoulder pain after surgery and radiation for throat cancer. From Safarpour and Jabbari 2018. Drawing by Dr.Damoun Safarpour. Printed with permission from Springer

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

Patient Example

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

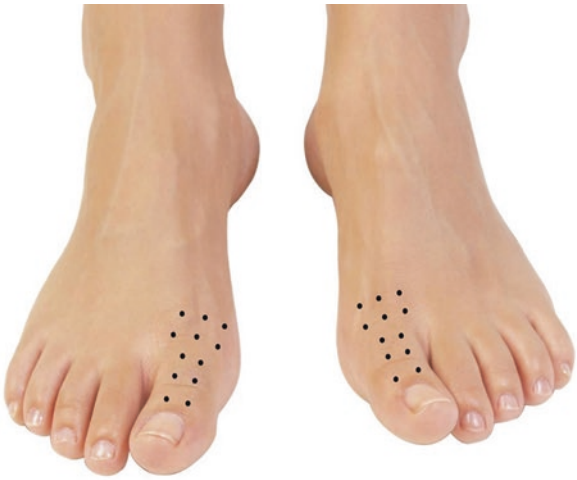

Fig. 17.7 sites of injection in the patient with cancer and neuropathic pain caused by an immune modifying drug

Prevention of Pain after Surgery

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

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

Temporomandibular Disorder

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

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

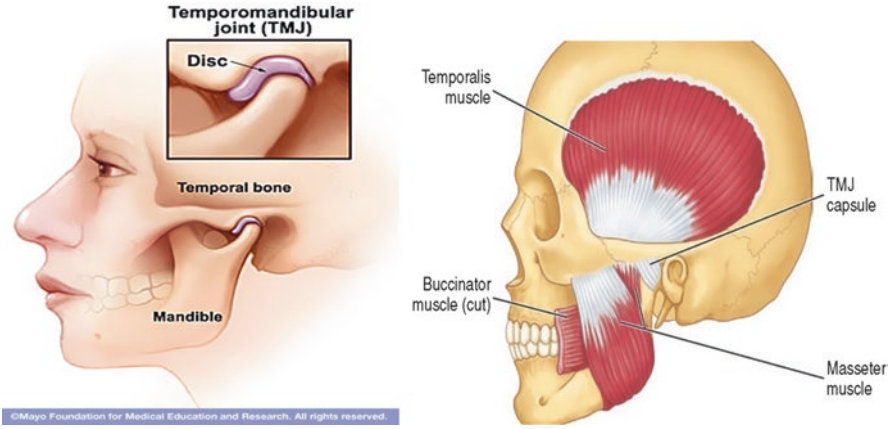

Fig. 17.8 Temporomandibular joint. Printed with permission from Mayo Foundation

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

Teeth Grinding (Bruxism)

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

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

References

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

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