Chapter 16
Botulinum Toxin in Dentistry and Treatment of Chronic Orofacial Pain

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Introduction

Pain, either acute or chronic, is a disturbing uncomfortable sensation with multiple aspects that afflicts individuals at different mental, psychological, and physiological levels [1]. Orofacial pain (OFP) is described as pain involving the hard and soft tissues of the face and all its related areas including the oral cavity [2]. In contrast to the acute type which is temporary, chronic pain does not subside after removal of a stimulus or healing of the injured region and is considered a disease by its very nature [1]. Pain persisting beyond 3 months is considered as chronic, which is a relatively common issue, affecting approximately 20% of people worldwide [3]. In the orofacial region, its prevalence is between 16.1% and 33.2%, with 10% qualifying as chronic [4]. Considering the distinctive anatomical, functional, and physiological features of the orofacial complex, in addition to the social and psychological elements associated with OFP, there is a strong need for further research in this area in order to introduce safe and effective treatment options to achieve optimal management strategies.

Chronic headaches and OFP are among the most common pain disorders known to clinicians. They have been classified by several systems and were included

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separately in the most recent version of the International Classification of Diseases (ICD-11), taking effect as of January 2022 [3, 5]. Generally, chronic OFP has been divided into musculoskeletal, neuropathic, neurovascular, and idiopathic subtypes with differing nomenclature used in different classification systems [1, 6–8]. Regarding the versatile mode of action of botulinum neurotoxin (BoNT), with its anticholinergic, analgesic, and anti-inflammatory effects, this toxin can be a safe and appealing option for treating diseases in each of these subclasses.

Adopting the style used by the International Classification of Headache Disorders, 3rd edition (ICHD-3) and aligned with ICD-11, the International Classification of Orofacial Pain (ICOP) has offered a detailed and elaborate classification with practical diagnostic guidelines [9] and has been used in most sections of the following text, where possible.

Chronic Orofacial Pain

Musculoskeletal Orofacial Pain

Chronic musculoskeletal pain arises from disorders or causes that involve bones, joints, muscles, and soft tissues [8]. Most facial pains have a musculoskeletal origin and encompass the area innervated by the maxillary and mandibular branches of the trigeminal nerve [5]. To describe this type of pain, terms like “deep,” “pressure,” “muscle tenderness,” and “dysfunction” have been used [7]. Conditions belonging to this subclass include masticatory myofascial pain, temporomandibular joint pain, tension-type headache, and cervical headache [6, 7]. The following text will concentrate on the two first subtypes, which will be presented collectively under the more recognized term, temporomandibular disorders (TMDs).

Temporomandibular Disorders (TMDs)

Definition, Classification, and Epidemiology

The term TMD refers to a group of painful and non-painful disorders involving the temporomandibular joint (TMJ), masticatory muscles, and adjoining structures [9]. It has been estimated that approximately 33% of the general population demonstrate at least one TMD symptom, that is, masticatory muscle tenderness and/or pain, TMJ sounds and/or pain, and restricted jaw opening [10]. Painful TMDs are the most common cause of OFP, and their annual incidence in the United States has been reported at 4%. They occur twice as often in women as in men and are more common in the second to fifth decades of life. Persistent pain has been reported in 49% of TMD patients [11]. Association with other comorbidities like migraine/headache, neck pain, fibromyalgia, irritable bowel, and lower back pain is not uncommon [12, 13].

According to ICOP, pain related to TMD can be found under myofascial OFP and TMJ pain [9]. The diagnostic criteria for myofascial OFP start with the initial

distinction between the two main subtypes: primary and secondary myofascial OFP, followed by further subdivisions, subtypes, and subclasses. Masticatory muscle pain, not assignable to another disorder, is considered "primary," while myofascial pain due to tendonitis, myositis, or muscle spasm is regarded as "secondary." Primary masticatory muscle pain can be episodic (30 min each and a total duration of ≥2 h/day) or continual/continuous and manifest in the jaw, temple, and ear vicinity. Its occurrence in the temporalis and/or masseter muscles needs to be confirmed by examination and should be provoked by palpation of one or both of these muscles and/or movements related to maximum jaw opening. It must also exhibit an increase or decrease in pain, following jaw movement, function, or parafunction [9]. Provocation of pain is determined by exertion of 1 kg pressure for 2 s, and referral or spread of pain is assessed through applying palpation pressure of 1 kg for 5 s [14].

Similarly, the diagnostic criteria for TMJ pain also include initially differentiating between primary and secondary subtypes, followed by further classification into comparable subtypes and subclasses. Primary TMJ pain is localized to the joint without any causative disorder and can occur with or without jaw movement or palpation. It involves episodic or constant pain inside and/or in front of the ear confirmed by examination indicating occurrence in one or both TMJs. It also should be provoked by palpation of the lateral pole of the condyle or its vicinity and/or by maximum jaw movement of any type, with modification of pain. Secondary TMJ pain is caused by other disorders like systemic or nonsystemic arthritis, degenerative joint disease, subluxation, or disc displacement with or without reduction and the possibility of intermittent locking [9].

Management of Temporomandibular Disorders

The treatment of TMD has a long history evolving from orthodontics for occlusion correction in the late 1990s to more invasive techniques like arthrocentesis or arthroscopy in early 2000 to physical, psychological, and pharmacological therapies during the past decade [15]. Injection of substances such as corticosteroids, hyaluronate, anesthetics, and BoNT is reserved for patients whose pain does not resolve after conservative treatments like counseling, medication, physiotherapy, and occlusal splints [15, 16]. Traditionally, BoNT has been administered intramuscularly for muscle relaxation leading to bite strength reduction and an indirect "joint-sparing effect" with consequent pain relief [17]. More recent evidence suggests axonal transport of BoNT to motor and sensory neurons from the peripheral to the central nervous system (CNS). Clinically, the antinociceptive effect of intramuscular BoNT injection is felt before muscle paralysis. Following soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) cleavage by BoNT at the injection site, there are significant reductions in inflammatory factors like IL-1ß, calcitonin gene-related peptide, and substance P [10, 18], making BoNT practical for short- and long-term TMD pain management.

In cases where TMD pain is related to TMJ issues, BoNT can decrease TMJ overload by relieving muscle tension, could be administered to treat cases associated with dislocations [19], and may be directly injected in the joint to exert an antinociceptive effect by blocking neurotransmitter release from primary sensory neurons [20]. Neuropeptides and cytokines in inflamed joints sensitize the local nerves. Pain relief in arthritis occurs following reduction of inflammation due to

neuropeptide inhibition. Intra-articular BoNT injection may have an anti-inflammatory effect through inhibition of neuropeptides/cytokines, reducing generation of its mediators like substance P, ultimately leading to diminished pain [21].

Efficacy of BoNT in the Treatment of Temporomandibular Disorders with Pain

BoNT Injection for TMD Pain Primarily Attributed to the Masticatory Muscles

Inactivation of neural transmission and acetylcholine blocking are BoNT features that have led to its approval for treating a variety of muscle disorders. In the orofacial region, the anti-inflammatory, muscle-weakening, and analgesic effects of this toxin have been exploited to treat TMD pain [22, 23].

Using the criteria of the American Academy of Neurology (AAN) [24, 25], the efficacy of BoNT-A in TMD-associated myofascial pain management can be given a Level B efficacy (*"probably effective"*) based on one class I study [23] and one recent class II trial [22].

The most recent high-quality, class II study is a randomized clinical trial by de la Torre Canales et al. [22], who evaluated the effectiveness and safety of BoNT-A in 100 women with persistent myofascial pain (47 had arthralgia or disc displacement in addition to myofascial pain). Five groups of 20 patients each received oral appliance, placebo, 80 U, 140 U, or 200 U onabotulinumtoxinA (Botox). All injections for subjects allocated to placebo/BoNT groups were administered in both masseter and temporalis muscles by an operator blind to the dilutions. Based on the results, the three doses of BoNT-A significantly decreased pain compared to placebo and were all as effective as oral appliances.

Using different quality assessment approaches like GRADE and Jadad, a number of systematic reviews/meta-analyses have reported the evidence of BoNT utility for TMD pain control to be moderate to low, and despite demonstrating improvements in patients, its efficacy has been stated to be unclear at the current time. The risk of side effects was reported as not significant. According to these reviews, some investigations support the better performance of BoNT compared to placebo in the short-term (1 month) follow-up, but not during longer intervals (3 and 6 months); a number of studies have reported BoNT to be equal to or slightly better than other treatment modalities, and yet others report no significant difference compared to controls or therapies like facial manipulation [26–28].

From 2017, among the investigations on BoNT efficacy in TMD pain, we analyzed nine studies that were either high quality [22, 23] and/or had used the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [14] for their patient selection [18, 22, 29–34]. To further minimize heterogeneity, TMD due to bruxism will be discussed separately, especially considering that not all patients with TMD have bruxism and vice versa [35]. There were three randomized trials, and the rest were either retrospective or prospective clinical studies (Table 16.1). A variety of BoNT doses, injection sites and numbers, assessment tools, and patient groups were reported. Injections ranged from 30 MU Botox injected into one to six muscles [30] to 200 U Botox injected into 20 sites in four muscles [22]. The shortest lasting effect was 30 days [18], while two studies reported longer relief periods of up to 6 months [22, 32].

Table 16.1 Outline of studies using botulinum toxin to manage myofascial pain related to temporomandibular disorders

Author/ year	Study type	Patients	BoNT	Dose	Injection	Assessment	Outcome	Diagnosis	Comments
Khawaja et al. 2017 [29]	Retrospective	$N = 116$	Botox (onaA)	100U	In painful muscles (masseter±temporalis); 2 cycles ≥12 w apart	11-point Likert-type scale	Sg pain relief for 10 w in 1/3 of patients	Refractory masticatory myalgia	Patients with Sg relief had Sg more AE
Abboud et al. 2017 [30]	Retrospective	$N = 25$ Localized: 13 Referring: 12	Botox	30–180 MU	Into 1–6 uni/bilateral painful muscles: masseter, anterior temporalis, sternocleidomastoid, and posterior digastric	Self-reported pain evaluation	Sg benefit of BoNT in patients with localized, but not referring MFP	MFP	AE: transient tenderness, asymmetric smile
Patel et al. 2017 [23]	Randomized controlled pilot	$N = 19$; Plc: 9 BoNT: 10	Xeomin (incoA)	170U	2 masseter (100U), 2 temporalis (50U), 2 external pterygoid muscle (20)	0–10 pain scale	Sg decrease of pain scores vs placebo	TMD	No adverse effects
Villa et al. 2018 [31]	Retrospective	$N = 28$	Botox	150U	2 masseter (100U) in 3 sites, and 2 temporalis (50U) in two sites	VAS (pain) OHIP-14 TMJ-QoL	- Sg decrease in VAS - Sg improved QoL	TMD	Sg effects seen in 1st and 3rd month
Montes-Carmona et al. 2020 [32]	Randomized, single-center clinical trial	$N = 60$ (20×3); Plc, lidocaine, BoNT	Botox	2 masseter: 48–60U 2 temporalis: 48U 2 lateral pterygoid: 16U 2 medial pterygoid 16U	Masseter (3×8–10U), temporalis (3×8U), lateral pterygoid (8U), and medial pterygoid (8U)	VAS (pain) Therabite® ruler (mand movements)	Sg better pain relief and movements in BoNT vs two other groups	MMFP	Sg results were more evident in "localized refractory MMFP" than referred types. Lasted 6 m No AE

(continued)

Table 16.1 (continued)

Author/ year	Study type	Patients	BoNT	Dose	Injection	Assessment	Outcome	Diagnosis	Comments
De la Torre Canales et al. 2020 [22]	Randomized, controlled clinical trial	$N = 100$ (20×3); oral appliance, Plc, low-, medium-, high-BoNT	Botox	Low: 80U; Medium: 140U; High: 200U 5 injections/ muscle, 5 mm apart	Low: 2 masseter (60U)+2 temporalis (20U), Medium: 2 masseter (100U)+2 temporalis (40U), High: 2 masseter (150U)+2 temporalis (50U)	VAS, PPT, EMG, MP, UI, CBCT	BoNT-A was more effective than Plc throughout 6 m and as effective as oral appliance over 24 w, regardless of the dose	MFP[a]	AE: reduced muscle activity and thickness + bone volume in high doses AE were dose-dependent and transient in low-doses
de Lima et al. 2021 [18]	Prospective, longitudinal	$N = 15$[b]	Botox	80U	Symmetrically in 4 points of each masseter and each temporalis, 20U/muscle	VAS (pain)	-Sg lower pain on day 15 vs baseline -Baseline values returned on day 30	TMD	Low-dose BoNT was effective, but short-lived No AE

Chaurand et al. 2021 [33]	Clinical trial	$N = 22$	Xeomin	100IU	15IU/trigger point in temporalis	VAS (pain), SF36	Sg pain relief: baseline vs 2 m; Sg QoL only at 2 m	Bilateral MFP + ≥4 trigger points/side and no joint issues	At 7 m, VAS and QoL inclined toward baseline No AE
Yoshida 2021 [34]	Clinical	$N = 53$	Botox	50–100U	Under EMG guidance, masseter, temporalis, medial/lateral pterygoid, posterior belly of digastric, and sternocleidomastoid with 3–6 m intervals depending on patient satisfaction	VAS	The mean improvement (0–100%), at the endpoint was 80.8% for MFP	TMD, no arthrogenous pathology	Minimum AE

AE adverse events, *BoNT* botulinum neurotoxin, *CBCT* cone-beam computed tomography, *d* day, *EMG* electromyography, *m* month, *MMFP* masticatory myofascial pain, *MP* masticatory performance, *NSg* nonsignificant, *OHIP-14* Oral Health Impact Profile questionnaire, *Plc* placebo, *PPT* pressure pain threshold, *QoL* quality of life, *SF36* short form (36), *Sg* significant, *TMD* temporomandibular disorder, *TMJ-QoL* temporomandibular joint replacement quality of life questionnaire, *TMJD* temporomandibular joint disorder, *UI* ultrasound imaging, *VAS* visual analog scale, *vs* versus *w* week

[a] Included subjects demonstrated myofascial pain ($N = 53$), myofascial pain/arthralgia ($N = 12$), myofascial pain/disc displacement with reduction ($N = 27$), and myofascial pain/disc displacement without reduction ($N = 8$)

[b] A total of 35 patients were evaluated in this study, 15 of whom had TMD

One of the reasons for the variability in BoNT application is that muscle size could impact the neuromuscular effect of BoNT. Therefore, bulkier and larger muscles would need more toxin to demonstrate the desired effects, and considering that muscle size is extremely variable among patients, the dosage of BoNT is adjusted on an "as needed" basis [36]. In addition, some studies modify the dosage according to the level of patient's complaint and symptoms [18, 34]. De la Torre Canales et al. [22] showed superior pain-controlling effects of BoNT-A compared to saline, regardless of its dosage. Considering that adverse events increase in patients who receive higher doses of the toxin, they suggested using the lowest possible dose, which would offer the same effect as higher dilutions. Relief seemed to be achieved through effects of both dose-dependent motor activity and antinociceptive effects of BoNT-A.

Another interesting observation among the evaluated studies was that BoNT had a better impact on patients with localized myalgia than those who suffered from referred myofascial pain. In individuals with this kind of pain, soreness extends to areas distant from the limits of the affected muscle (DC/TMD) [30, 32].

BoNT Injection for TMD Pain Primarily Attributed to Temporomandibular Joint Origin

TMD pain with arthrogenic origin has also been managed by BoNT-A (Table 16.2). In a clinical study, significant improvement was observed after bilateral injection of 300 U and 200 U Dysport into the masseter and temporalis muscles, respectively, of 13 patients with pain due to disc disorder and degenerative joint disease [37]. Thomas and Aronovich [38] injected 53 subjects with TMJ arthralgia and refractory arthrogenous and myogenous pain with placebo or Botox before arthroscopy and found better pain relief in those who had received BoNT-A. In a prospective cohort study [39], intraoral versus extraoral approach for electromyography (EMG)-guided BoNT-A injection into the lateral pterygoid muscle was tested in 20 joints of patients with anterior disc displacement with reduction. For extraoral injections, insertion was through the space formed by the zygomatic arch and the mandibular sigmoid notch below the center of the zygomatic arch in patients with closed mouths. The intraoral insertion point was above the upper molars, parallel to the occlusal plane and lateral to the maxillary tuberosity. Pain reduction was significant compared to baseline in both groups, but the intraoral approach took significantly less time and was better tolerated by the patients. As stated above, de la Torre Canales et al. [22] included 12 and 35 patients with arthralgia and disc displacement (± reduction) in their randomized clinical trial of 100 TMD cases and reported favorable results of BoNT-A injection into the temporalis and masseter muscles, even in low doses.

Another method for pain control in arthrogenic TMD is through intra-articular administration of BoNT. Animal studies have demonstrated that injection of Botox into rat TMJs can prevent neuropeptide release leading to decreases in persistent hypernociception related to albumin-induced arthritis [40]. Batifol et al. [20] conducted a retrospective study on 77 patients with severe chronic TMJ pain who had not responded to any treatments including intramuscular BoNT and intra-articular

Table 16.2 Summary of studies on the use of botulinum neurotoxin in temporomandibular joint-related pain management

Author/ year	Study type	Patients	BoNT	Dose	Injection	Assessment	Outcome	Diagnosis	Comments
Kim et al. 2016 [37]	Clinical study	N = 13[a]	Dysport® (aboA)	500U	Masseters (2 × 150U) +temporalis (2 × 100U) in three sites, 1cm apart	Pain intensity, disability points, chronic pain grade, depression index, grade of nonspecific physical symptoms	Sg pain relief pre- vs post-treatment	Disc disorders, degenerative joint diseases, osteoarthritis, and osteoarthrosis	
Thomas and Aronovich 2017 [38]	Retrospective cohort	N = 52 BoNT:30, Control: 22	Botox	≤50U/each masseter, ≤25U/each temporalis	Based on tenderness, 5, 10, or 15U were injected	MRI, VAS	Sg greater decrease of pain in BoNT vs control	Refractory MFP with arthrogenous and myogenous pain	BoNT was evaluated as an adjunct to arthroscopy
Batifol et al. 2018 [20]	Retrospective	N = 77	Botox	30U/joint	Posterior-superior condylar border in the joint space	VAS (pain), mouth opening, SF36	Sg pain relief baseline vs. 15 d, 1 m and 3 m, NSg changes in mouth opening Improved QoL	Severe, chronic, refractory TMJ pain, nonresponsive to all treatments	Intra-articular BoNT is not effective for mouth opening Transient AE
Altaweel 2019 [39]	Prospective cohort study	N = 20 joints Intraoral: 10 Extraoral: 10	Botox	20IU/ muscle	EMG guidance for LPM injection by intra- or extra-oral approach	MRI (clinical Dx) VAS (pain) EMG (LPM activity)	Sg pain relief in both groups vs baseline Sg tolerability in intra>extra Sg larger mean time in extra vs intra	ADDWR	Pain relief from 4th week lasting to 24th week in both groups

ADDWR anterior disc displacement with reduction, *AE* adverse events, *BoNT* botulinum neurotoxin, *Dx* diagnosis, *EMG* electromyography, *LPM* lateral pterygoid muscle, *MFP* myofascial pain, *MRI* magnetic resonance imaging, *NSg* nonsignificant, *Plc* placebo, *QoL* quality of life, *Sg* significant, *TMJ* temporomandibular joint, *VAS* visual analog scale, *vs* versus, *w* week

[a] Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) was used for the diagnosis of 21 TMDs, who were further classified by the Japanese Society for the Temporomandibular Joint criteria, after which there were five patients with disc disorder and eight with degenerative joint diseases, osteoarthritis, and osteoarthrosis, some may or may not have had parafunctional habits

sodium hyaluronate injections in the past 4 months. In an aseptic room, 30 U of Botox was injected into the joints following subcutaneous anesthesia. Doses of 20 U, 30 U, and 50 U were previously tested by the investigators, and 30 U was found to be optimal. Clinical significance was set at a two-point reduction of pain on visual analog scale (VAS), which was observed in 66% of the patients at 1 month, lasting up to the 3rd month post-injection. Improvements in mouth opening and quality of life were also noted.

Comment

BoNT-A has shown positive effects in reducing pain and discomfort of TMD patients, and its tolerability and minimal adverse events (especially in low doses) make it suitable for treatment of this disorder. Based on AAN criteria, BoNT-A is *"probably effective"* for the treatment of pain in TMD. Double-blind, placebo-controlled, class I clinical trials with extended follow-up periods may provide further evidence to establish the use of BoNT as *"effective."*

Considering the multifactorial nature of TMD pain, the first step in rendering a treatment plan would be to reach a diagnosis and attempt to identify its major attributable source(s), that is, myogenous or arthrogenous. For intramuscular injections, it is best to consider the bulk and size of the muscle and to use the lowest dose possible with 30 day recalls to evaluate the possibility of further rounds of treatment. Planning should be individualized for each patient while contemplating additional treatment options in those affected by referred myofascial pain. Considering the lack of information on intra-articular injections, they should be saved as a last resort and only if the operator has the necessary skills to perform a safe injection.

Bruxism

Definition, Classification, and Epidemiology

Bruxism, generally classified as sleep and awake subtypes, is an oral movement disorder encompassing a range of facial muscle activities of various causes and clinical relevance. In 2013, a multidisciplinary group of experts gathered to form a consensus on its definition and diagnostic criteria [41], which was later updated in 2018 [42]. Sleep and awake bruxism were respectively described as "masticatory muscle activities that occur during sleep (characterized as rhythmic or nonrhythmic) and wakefulness (characterized by repetitive or sustained tooth contact and/or by bracing or thrusting of the mandible)" in otherwise healthy individuals. Clenching was considered as "teeth touching not for swallowing purposes" and bracing/thrusting as "increased levels of masticatory muscle activity without tooth contacts" [42]. Sleep bruxism has been reported to occur in 7.4% of the population, and the prevalence of awake bruxism is recorded as 22.1–31% [10]. However, their true incidence remains unknown [35].

Bruxism may be harmless and have one or more negative consequences or even be a protective behavior [42]. It is clear that treatments are directed toward the second situation in which bruxism is a risk factor for inducing harmful events like orofacial pain.

Assessment of bruxism includes noninstrumental and instrumental approaches. Examples of the former are questionnaires, oral reports, and clinical examination. The latter consists of EMG recordings and polysomnography ideally coupled with audio/video recordings. Due to the multifactorial nature of the disorder, a reliable cutoff for types that pose as a risk factor is not practical [42, 43]. Both types of bruxism are graded as *possible*, *probable*, and *definite* according to (1) self-report only (minimum recording of one or 2 weeks), (2) clinical examination±self-report, and (3) instrumental determination±self-report±clinical examination, respectively [42].

Management of Bruxism

Clinical consequences of bruxism include occlusal wear, tooth damage, implant complications, and muscle or joint pain, but there is no agreement on which of them necessitate treatment of the behavior [35, 42, 43]. Both types of bruxism have shown correlation with TMD pain [44], but the possibility that they are a direct cause of TMD pain has not been conclusively established [45], and their amount and intensity do not necessarily result in increased muscle overloading and more pain [35, 46]. The need for interventions appears to be related to the extent of behavior-related harm detected by the physician and the patient's complaint. Pharmacotherapy (e.g., tricyclic antidepressant, protein pump inhibitors, BoNT injections); electromyography, biofeedback, and transcutaneous electrical neuromuscular stimulation; occlusal devices; muscle stretching; and combination approaches have been used with inconsistent results and questionable long-term effectiveness [10, 35].

Efficacy of BoNT in the Treatment of Pain Associated with Bruxism

The first report of BoNT injection for the treatment of bruxism was in 1990 [47]. A 32-year-old woman who had developed bruxism while recovering from a coma following a car accident 6 month earlier was injected with 25 U of toxin-hemagglutinin complex of botulinum toxin into both temporal and masseter muscles after partial recovery from her coma. A significant decrease in her bruxism was observed which lasted for 8 weeks with no effect on or interference with patient's feeding [47].

The most important aspect of bruxism that leads to clinical consequences necessitating treatment is "masticatory muscle activity" [42]. Therefore, a reasonable approach to its management would be to decrease the activity of masticatory muscles in a safe way, without compromising their physiological functions. BoNT enters nerve endings in the neuromuscular junctions, where it inhibits acetylcholine

release from synaptic terminals through cleaving SNAREs which results in reduced muscle contraction [10]. The effects are usually noticeable within a few days to 1 week. The highest point of efficacy occurs after five to six weeks, and gradual decrease is seen thereafter, returning to its pre-injection state, 12 weeks after injection [48]. In an animal study, 1 month after BoNT administration into the masseter of rabbits, a reduction in amplitude and duration of EMG was observed with concomitant histologic atrophy of muscle fibers and increased collagen. After 3 months, some innervation had occurred as demonstrated by normal EMG duration and slightly increased cell division and fiber regeneration. However, microscopically some deficits including hypertrophied/atrophied/dead fibers and fibrosis remained [49]. In addition to its paralyzing effect on the masticatory muscles, BoNT may also have an antinociceptive effect in bruxism cases associated with pain (see Management of Temporomandibular Disorders above).

An interesting speculation regarding BoNT application in bruxism was that the feedback loop of the trigeminal motor nucleus might be affected by toxin-provoked muscle paralysis leading to suppression of the "central bruxism generator" [50]. Similarly, it was proposed that the peripheral effect of BoNT may have a central diminishing consequence, either directly or by decreasing central input following reduction of peripheral activity [48]. The central and autonomic nervous systems have been suggested to have a role in generating phasic or tonic (rhythmic or non-rhythmic) masticatory muscle activity during sleep. It has been hypothesized that brain chemicals may control sleep-associated events and airway patency during sleep and enhance rhythmic masticatory muscle activity (RMMA) that occurs prior to sleep bruxism (SB) episodes [51].

Based on recent studies on BoNT-A administered to bruxers with pain (Table 16.3) [18, 50, 52–57], it seems that this toxin as a minimum can reduce bruxism-associated pain.

The literature (Medline and Google Scholar search) includes two class II studies [53, 54] and one class 1 trial [50] that have shown significant decrease in pain, providing level B evidence indicating BoNT to be "*probably effective*" for pain management in bruxers. Almost all studies used onabotulinumtoxinA (Botox), which was injected into the masseter (40–48 U) or masseter+temporalis (80–100 U) muscles into 3–4 points. Effects were reported as soon as 12 days post-injection [52], and minimum return to baseline values was 90 days [18], while significantly less pain was reported even at 24 weeks in patients injected with BoNT compared to saline [50]. Most of the studies evaluated SB and used questionnaires/self-reports and examination. In comparison between BoNT and occlusal splints in a randomized single-blind prospective trial on 73 patients, Yurttutan et al. [53] reported significant decrease of pain by both approaches; however, patients receiving BoNT and BoNT+occlusal splint had significantly less pain compared to those with occlusal splints only, while no differences were found between the BoNT groups. They suggested no added benefit of occlusal splints, especially considering the difficulties in their application and the need for long-term compliance due to their relatively late-onset effects. BoNT was ultimately proposed as an effective treatment for bruxism-related pain with limited need for commitment and long-term results. Kaya and

Table 16.3 Recent studies using botulinum toxin to manage orofacial pain in patients with sleep and/or awake bruxism

Author/ year	Study type	Patients	BoNT	Diagnosis	Dose	Injection	Assessment	Outcome	Comments
Asutay et al. 2017 [52]	Retrospective data analysis	*N* = 25	Botox	SB (clinical)	40 MU	Origin, insertion, ant, and post masseter (5 MU/site)	VAS, 0, 2 w, 1 m, 3 m, 4 m, 6 m	Sg pain reduction except between 2 w vs 4 m and 1 m vs 3 m; Max mouth opening: no changes	Mean effect onset: 12 d Mean loss of effect: 4.8 m No AE
Jadhao et al. 2017 [57]	Double-blind, placebo controlled, randomized clinical trial	*N* = 24 Saline: 8 BoNT: 8 None: 8	Botox	SB (self-report, examination)	100U	Masseters (30U/side) and temporalis (20U/ muscle, in 3 points)	VAS (pain at rest and chewing), and occlusal force analysis 0. 1 w, 3 m, 6 m	VAS decreased only in BoNT group Sg decrease in occlusal force in BoNT vs saline and control	Lowest level of occlusal force was in 3rd m after BoNT
Al-Wayli 2017 [55]	Randomized controlled parallel group clinical trial	*N*=50 BoNT: 25 Other treatments: 25	Botox	"Probable" SB[a] with bilateral masseter pain	40U	Masseter (20U/side in 3 points)	VAS, 3 w, 2 m, 6 m, 1 y	Sg decrease in mean pain score in BoNT vs conventional group at all time points No improvement in conventional treatment	Suggestion: evaluation 15 d after injection and control after 3–4 m for repeat if necessary
Ondo et al. 2018 [54]	Randomized double-blind, placebo-controlled followed by open-label	*N* = 22 Saline: 9 BoNT: 13	Botox	SB (questionnaires, examination, PSG using ICSD-3 criteria)	200U	Masseters (60U/ muscle in 2 points) and temporalis (40U/ muscle, in 3 points)	1st efficacy endpoint: CGI, 2nd endpoint: VAS of change in bruxism and pain 4–8 w after injection	CGI and VAS of change, both Sg favored BoNT	Two BoNT patients reported cosmetic smile change

(continued)

Table 16.3 (continued)

Author/ year	Study type	Patients	BoNT	Diagnosis	Dose	Injection	Assessment	Outcome	Comments
Yurttutan et al. 2019 [53]	Randomized, single-blinded, prospective	*N* = 73 OS: 25 BoNT: 24 BoNT+OS: 24	Botox	Myofascial pain due to bruxism (RDC/TMD, questionnaire)	90U	2 masseters (5 × 6U in each); 2 temporalis (3 × 5U in each)	TMD-PS, GCPS, OBC, JFLS, and VAS (muscle palpation), 0 and 6 m	Sg VAS decrease in all groups Sg VAS decrease in both BoNT groups vs OS-only group, but not between BoNT groups	One patient excluded for asymmetric smiling
de Lima et al. 2021 [18]	Prospective, longitudinal	*N* = 20[b] SB: 12 AB: 8	Botox	Pain (DC/TMD) due to SB and AB (self-reports, clinical exams using ICSD)	80U	Symmetrically in 4 points of each masseter and each temporalis, 20U/ muscle	VAS (pain), 0, 15, 30, 60, 90, 180 d	-Sg lower pain on day 15 vs baseline -Baseline values returned on day 90	No AE
Kaya and Ataoglu 2021 [56]	Prospective, randomized, clinical trial	*N* = 40 OS: 20 BoNT: 20	Botulinum toxin type A	Myofascial pain due to bruxism (referred patients, examination)	48U	Masseter: 24U/side, 8U/point	VAS (pain), modular system (max BF), 0, 2 w, 6 w, 3 m, 6 m	VAS reduction in both groups, no Sg difference In BoNT, BF decreased in 2nd and 6th weeks, but was not different in 3rd and 6th months vs day 0 In OS, BF only increased in 6 m	

M Alwayli et al. 2021 [50]	Prospective, double-blind, randomized	*N* = 40 Saline: 20 BoNT: 20	Botox	"Probable" sleep/awake bruxism[a]	40U	Masseters (20U/side, 5U in 4 points)	VPS (pain at rest and chewing) 0, 2, 4, 8, 12, 16, 18, and 24 w	Sg decrease in VPS after 2 w in BoNT Mean difference of VPS increased from 8–24 w in BoNT Sg less pain at 2, 8, and 24 w in BoNT vs saline	No AE

AASM American Academy of Sleep Medicine, *AB* awake bruxism, *AE* adverse events, *ant* anterior, *BF* bite force, *BoNT* botulinum neurotoxin, *CGI* clinical global impression, *d* day, *DC/TMD* Diagnostic Criteria for Temporomandibular Disorders, *EMG* electromyography, *GCPS* Graded Chronic Pain Scale: *IAF* Fonseca anamnestic index, *ICSD* International Classification of Sleep Disorders, *JFLS* Jaw Function Limitation Scale, *Max* maximum, *m* month, *OBC* Oral Behavior Checklist, *OS* occlusal splint, *PSG* polysomnography, *post* posterior, *RDC/TMD* Research Diagnostic Criteria for Temporomandibular Disorders, *RMMA* rhythmic masticatory muscle activity, *SB* sleep bruxism, *Sg* significant, *TMD-PS* Temporomandibular Disorder Pain Screener, *VAS* visual analog scale, *VPS* visual pain scale, *y* year

[a]Based on 2013 consensus criteria (reference 40)

[b]A total of 35 patients were evaluated in this study, 15 of which had TMD with no bruxism, detailed in Table 16.1

wAtaoglu [56] also compared these methods in 40 patients and found no difference in the reduction of pain between the two groups. In contrast to Yurttutan et al. [53], who administered BoNT to both masseter and temporalis muscles, they only injected the masseters and did not include a BoNT+occlusal splint group. Nonetheless, they proposed using BoNT in patients who cannot use occlusal splints. It has been suggested that BoNT injection may be even more useful in bruxers with clinical consequences other than pain, since their cooperation to use occlusal splints may be even less, due to the lack of a strong incentive like pain [48].

Notwithstanding the foregoing, it has been indicated that the effect of BoNT may be mainly subjective and it may not have a major impact on reducing the actual number of episodes and the genesis of RMMA and bruxism [58, 59]. The perceived effect by the patient is probably due to the lowering in masseter intensity as evidenced by EMG data [58]. Further controlled studies objectively measuring outcomes like muscle forces, sleep variables, and bruxism events have been proposed [48, 59].

Comment

Based on several high-quality studies in the literature and using the AAN criteria, BoNT-A is *"probably effective"* for the management of patients with bruxism-related pain, successfully providing them with relief. BoNT can be applied as a substitute for occlusal splints, which require high maintenance and can be uncomfortable, in addition to demonstrating late-onset effects. This toxin can even be prescribed to bruxers that have clinical consequences other than pain. Larger class I trials with longer follow-up on bruxers with pain are required to provide level A evidence for the application of BoNT in controlling pain in individuals with bruxism.

Neuropathic Orofacial Pain

By definition, neuropathic pain refers to allodynia, hyperalgesia, and/or numbness of the skin, viscera, and musculoskeletal system directly caused by a disease/injury to nerves or structures of the CNS. It may be similar to pain felt during inflammation, but the distinction is that it must involve neural tissues. Its prevalence has been estimated at 6.9–10% of the population and is described as burning, sharp, or electric [1, 5, 7].

Neuropathic OFP is a blanket term used to cover painful lesions/diseases of the cranial nerves [1, 5]. ICOP has used the term "orofacial pain attributed to lesion or disease of the cranial nerves" and divided the clinical entities that fall under this category into those related to the trigeminal, or the glossopharyngeal nerves.

Pain Attributed to Lesions or Diseases of the Glossopharyngeal Nerve

Glossopharyngeal Neuralgia (GN)

Definition, Classification, and Epidemiology

GN is described as sudden, short, unilateral, shock-like, or stabbing severe pain lasting from a few seconds to 2 min in the area innervated by the glossopharyngeal and the auricular and pharyngeal branches of the vagus nerve, which is felt in the ear, tongue base, tonsillar fossa, and the mandibular angle, incited by jaw movements like swallowing, talking, and coughing. The classic type is diagnosed by MRI or during surgery, while secondary GN is characterized by an underlying disease causing neuralgia. It is extremely rare, affecting approximately 0.2–0.8/100,000 individuals per year, mostly men over 50 years of age [7, 9, 60].

Management of Glossopharyngeal Neuralgia

Pharmacotherapy including agents like carbamazepine, gabapentin, and pregabalin is the first line of treatment in GN management and could be supplemented with a glossopharyngeal nerve block, which has demonstrated favorable results. Surgical intervention is preserved for cases not responding to these options [60].

Efficacy of BoNT in the Treatment of Glossopharyngeal Neuralgia

We only found one publication on BoNT application in GN, which reported that neither Dysport nor Botox show any effect on pain control [61].

Comments

Until further studies on the efficacy of BoNT on GN are conducted, we cannot comment on its efficacy in reducing pain intensity in these patients. The only study in this regard did not show a positive effect of BoNT.

Pain Attributed to Lesions or Diseases of the Trigeminal Nerve

Trigeminal Neuralgia (TN)

Definition, Classification, and Epidemiology

According to ICOP, TN is characterized by recurring, unilateral, short, electric, shock-like pains, precipitated by innocuous stimuli that appear and cease suddenly and are limited to the distribution of one or more divisions of the trigeminal nerve. The pain is of severe intensity, and the attacks last from a fraction of a second up to 2 min. They occur inside the trigeminal dermatome with no radiation [9].

Its subtypes include classical or primary, secondary (due to multiple sclerosis, space-occupying lesion, other causes), and idiopathic [9]. According to the European Academy of Neurology (EAN), the difference between classical and idiopathic is that classical occurs as a result of "neurovascular compression with morphological changes of the trigeminal root," while idiopathic has "no neurovascular contact (NVC) or NVC without morphological changes of the trigeminal root" [62]. For diagnosis, close collaboration between neurologists, neuroradiologists, and dentists using MRI with or without diffusion tensor imaging, brain gray matter analysis, and trigeminal reflexes is recommended [62, 63]. The symptomatology is basically the same in all three subtypes [63].

TN occurs more commonly in women, rarely before 40 years of age, with an incidence that ranges between 0.03% and 0.3% in the general population, with higher incidence rates reported in the United Kingdom (27/100,000/year) compared to the United States (4/100,000/year) [64].

Management of Trigeminal Neuralgia

Pharmacological treatment is the first line of therapy for long-term TN pain, which includes carbamazepine, oxcarbazepine, and other anticonvulsant drugs. In addition to ¼–½ of patients becoming refractory to pharmacotherapy, there are a number of side effects associated with these drugs. Surgical options like microvascular decompression, gamma-knife surgery, and neuro-ablative therapy are offered after the failure of medical treatments. While their possibility should be mentioned in the early stages of treatment, the patient should also be made aware of their potential to cause side effects. Another safer and more acceptable therapy is BoNT-A injection, which is included in the 2019 guideline of the EAN on trigeminal neuralgia, to be used as add-on therapy for medium-term management. This is an important addition considering the high rate of persistent symptoms or side effects following application of carbamazepine and oxcarbazepine [10, 62, 63, 65].

Efficacy of BoNT in the Treatment of Trigeminal Neuralgia

The exact mechanism by which BoNT controls TN pain is uncertain. Both central and local/trigeminal antinociceptive effects have been suggested. Studies show that the antinociceptive activity of BoNT following its peripheral administration is due to a decrease in central sensitization and suppression of overexpression of nociceptors [66]. Additionally, the axonal transport of this toxin to the CNS can also contribute to its analgesic effects [10].

Matak et al. [67] evaluated the central antinociceptive function of BoNT-A in a formalin-induced model of facial pain. Their study included injection of low doses of toxin into the whisker pad and sensory trigeminal ganglion of rats. Colchicine was used as an inhibitor. They showed that trigeminal sensory neurons are responsible for axonal BoNT transport which is a requisite for its antinociceptive effects, even when directly administered to the ganglion. The conclusion was that the sensory root is the path by which BoNT-A is transmitted to the trigeminal nociceptive

projections in the CNS. Similarly, in a rat TN model based on chronic constriction injury of the infraorbital nerve, the antinociceptive effect of peripherally administered BoNT-A was attributed to its direct action on the trigeminal nucleus through axonal transport. The expression of some of the TRP family members (nonselective cation channel proteins) was downregulated, and central sensitization was decreased [68]. A recent animal study on rats indicated that injection of BoNT-A into the orofacial area reduces pain via axonal and hematogenous transport. Using a chemotherapy-induced bilateral neuropathic pain model, the authors showed that following unilateral peripheral administration of BoNT-A, the head withdrawal threshold was enhanced bilaterally. They also used an infraorbital nerve constriction model to demonstrate intensified head withdrawal threshold after peripheral toxin injection in the contralateral side. Another interesting observation was that intradermal injections resulted in the appearance of BoNT-A in the circulation. Finally, they reported identifying the C-terminal half of the heavy chain of BoNT-A in the neurons of both right and left trigeminal ganglia following unilateral peripheral injection [69]. Further studies are required to elucidate the exact mechanisms involved in the antinociceptive effects of BoNT.

Based on recent systematic reviews and meta-analyses, current evidence suggests that BoNT-A application in TN is an effective and safe option for reducing pain intensity and frequency with minimal transient side effects [70–73]. However, high-quality studies providing high level of evidence for its widespread usage in this disease are still lacking [36, 70–74]. Since the last edition of this book with one reported class I trial on TN [75], 12 studies [65, 76–86] and several case reports [74] have been added to the literature, of which two are class I double-blind, randomized, placebo-controlled studies [76, 78] (Table 16.4), conferring Level A evidence for BoNT efficacy in TN treatment. There are still no guidelines providing definitive specifications for dosage, injection site, number of injections, administration route or number, and time of repeats.

Dosage and number of injection sites has ranged from 15 IU [83] to 200 U [65] and 1 [84, 86] to 25 points [77, 81, 85], respectively. The lowest dose reported in the literature seems to be from an open-label trial on 13 patients, which found 6.45–9.11 U to be effective, depending upon the pain distribution area [87]. Short-term efficacy has been reported to be similar between higher (75 U) and lower doses (25 U) of BoNT [78]. Comparable effectiveness of small and large doses has also been confirmed in other studies [65, 77]. In addition to dosage, it is interesting that repetition of injections also did not affect therapy results. Neither treatment outcome nor side effects were different in single versus repeated injections, and adverse events were suggested to be more closely associated with the injection method [81].

The administration route has been mostly intradermal, or intra mucosal in trigger points (if identifiable) or along the distribution of the affected nerve and usually involves multiple points [77–79, 81–83, 85]. An open-label trial used a different approach that included only one or two injections by which BoNT was administered into the maxillary and/or mandibular nerve roots near the ganglion. The maxillary root was targeted through the upper edge of the zygomatic arch between the orbital rim and ear, while the middle of the lower edge of the zygomatic arch was the

Table 16.4 Overview of studies[a] using botulinum neurotoxin in the management of trigeminal neuralgia

Author/year	Study type	Patients	BoNT	Dosage	Injection	Assessment	Outcome	TN	Comments
Zúñiga et al. 2013 [76]	Double-blind, randomized, placebo-controlled	*N* = 36; BoNT: 20 Plc: 16	Botox (onaA)	50U	Subcutaneous; 1cm apart, along branch(es) + 10U in masseter for V3 involvement	VAS (pain), functional impact score, paroxysm (N), SF36	Sg decrease at 3 m in pain and paroxysm No Sg change in functional impact and SF36	Essential IASP, 1994	Synergistic effect of BoNT with other meds was reported
Li et al. 2014 [77]	Open-label	*N* = 88	HengLi® Lanzhou	25–170U	Intradermal &/or intramucosal in trigger points; 15 mm apart (total, 15–25 points with 2.5–5 IU/point, less for gum)	VAS (pain extent), attack frequency and side effects, PGIC	Effectiveness was 100% at 2 m and decreased to 38.6% at 14 m	One-branch classical	Effectiveness: percentage of patients with ≥50% reduction in VAS. Mild and transient AE
Zhang et al. 2014 [78]	Double-blind, randomized, placebo-controlled, parallel group	*N* = 84, BoNT 75U: 29, 25U: 27 Plc: 28	Lanzhou	25U or 75U	Intradermal and/or submucosal, at pain site; 20 points with 0.05 ml/site	VAS (pain severity), PGIC, AE, attack frequency	Sg improved VAS, PGIC, and efficacy in both BoNTs vs Plc No Sg changes between 25U vs 75U	Classical ICHD-II	Effectiveness: patients with ≥50% reduction in VAS. Mild-moderate and transient AE gone in 6 w
Xia et al. 2016 [79]	Open-label	*N* = 87	HengLi® Lanzhou	NS	Intracutaneous in trigger points or in pain distribution area: 15 mm apart (total, 15–20 sites)	VAS, side effects, SF-36, and sleep interference-, HAMA-, and HAMD-scores at 1, 2, 4, and 8 w	Sg improved VAS (all times) Sg improved efficacy at 1 w vs 2 w Sg improved anxiety and depression Sg improved sleep (all times) Sg improved QoL at 8 w[b]	TN	Effectiveness: patients with VAS reduction rate ≥50% Mild AE gone in 6 w

Türk Börü et al. 2017 [80]	Open-label	N = 27	Botox	50U for each root	Maxillary and/or mandibular roots; repeated if required	VAS (pain severity), attack frequency (N/d) and PGIC	Sg improved VAS and attack frequency at 1 w, 2 m, 6 m Effective response (88.9%) at 6 m -PGIC: 85.1% improved "very much" or "much"	Classical ICHD-2	Effectiveness: ≥50% VAS decrease from baseline to 6 m Transient facial weakness (N = 1); permanent masseter weakness (N = 2)
Zhang et al. 2017 [81]	Open-label	N = 81; Single dose: 44 Repeated dose: 37	Lanzhou, China	Single dose: 70–100U; Repeated dose: 50–70U, exactly repeated after 2 w	Intradermal and/or intramucosal at pain site; multiple: 15 mm apart (total, 15–25 sites with 1.25–5 U/site)	VAS (pain), attack frequency, time between treatment and effect, time to peak effect, and AE	No Sg difference in all factors at 6 m between single and repeated doses Sg longer duration of efficacy in single dose	Classical ICHD-2	Mild-moderate AE
Gorimanipalli et al. 2017 [82]	Retrospective observational	N = 23	Botox	Total of 54 injections in all 23 patients	Intradermal or submucosal in trigger points or pain distribution area: 3IU/cm^2 of pain area	VAS (pain intensity), days to onset of relief, weeks of relief	Sg improved VAS at 3 m 100% response; Mean duration of maximum relief: 26 w	Classical ICHD-2	Response: >50% pain relief -Only minor AE
Liu et al. 2018 [65]	Open-label	N = 43; ≥80 y: 14, <60 y: 29	Lanzhou, China	45–150U in older and 30–200U in younger	Intradermal and/or intramucosal in trigger zones	VAS (pain severity)	Sg lower VAS at 1 m than at baseline in both groups	Classic idiopathic ICHD-II	Mild-moderate AE, gone in 3 w

(continued)

Table 16.4 (continued)

Author/year	Study type	Patients	BoNT	Dosage	Injection	Assessment	Outcome	TN	Comments
Caldera et al. 2018 [83]	Observational	$N = 22$	BTX-A	15–50IU	Directly in trigger point or intradermal in pain distribution area	VAS (pain) at 10, 20, 30, 60, and 90 d	Sg improved VAS at all times No Sg difference between high vs low doses No Sg difference between trigger point vs pain distribution area	TN ICHD-II	BoNT was given as adjunct to medical therapy Maximum response: at day 60 post-BoNT No serious AE
Crespi et al. 2019 [84]	Prospective, open-label	$N = 10$ (one excluded for efficacy outcomes)	BoNT-A	25IU	Percutaneous navigation-assisted toward SPG	NRS (attack intensity), AE, PGIC, N of attacks, and function level at 0 and 5–8 w	Sg improvement in NRS and % of the day with persistent pain: No Sg improvement in attack N	Refractory classical ICHD-3b	Main efficacy endpoint: ≥50% reduction in median attack N/days between baseline and 5–8 w AE gone in 1 m
Zhang et al/2019 [85]	Follow-up retrospective study	$N = 152$	HengLi® Lanzhou	Low dose: <40U, Medium dose: 40–70U, High dose: >70U	Intradermal and/or intramucosal in trigger points; multiple: 15–20 mm apart (total, 15–25 sites with 1.25–5 U/site). Repeated if not improved after 2 w	VAS (pain extent), AE	Overall effective rate: 89.4%; Disease course and branch N, but not injection N affected incidence of side effects	Classical ICHD-2	Overall effective rate: % of patients with reduction by ≥50% Effective for 28 m suggests long-term control Clinical response may be patient-specific

Yoshida/2020 [86]	Open-label	$N = 10$	Botox	50U	SPG with CAD/CAM-derived injection guide	VAS (pain severity) & frequency at 0, 2 w, 4 w, 8 w, and 12 w	Sg improved VAS and pain frequency between baseline and endpoint All patients responded	Classical ICHD-3b	Responders: ≥50% reduction in VAS and pain frequency from baseline to endpoint No AE

AE adverse events, *BoNT* botulinum neurotoxin, *d* day, *HAMA* Hamilton Anxiety Scale, *HAMD* Hamilton Depression Scale, *ICHD* International Classification of Headache Disorders, *m* month, *NRS* numeric rating scale, *NS* not specified, *PGIC* Patients Global Impression of Change, *Plc* placebo, *QoL* quality of life, *SF36* short form (36), *Sg* significant, *SPG* sphenopalatine ganglion, *VAS* visual analog scale, *w* week

[a]Since the previous edition

[b]Except for physical function

insertion point for the mandibular root with predefined depths and needle rotations. The treatment was well tolerated, and 88.9% of the patients showed ≥50% reduction in pain in the 6th month, and 2 out of 17 patients were recurrence-free for 2 years [80]. This technique does not require a radioscopic or echographic guide but depends on the operator's skill.

Another injection option is the administration of BoNT toward the sphenopalatine ganglion. This method has been applied using a navigation device (MultiGuide®, aided by surgical navigation) [84] and a CAD/CAM-derived injection guide [86] on ten patients in each study. The latter study achieved response by all participants, whereas the former observed a significant reduction in attack intensity but not in its main efficacy endpoint, which was ≥50% reduction in median attack numbers per day.

Comments

Despite the "A" level of evidence for the effective use of BoNT in TN treatment [88], a guideline describing optimal doses, administration routes, number of injections, etc. is yet to be developed. To prevent side effects, tolerance, patient discomfort, and increased cost, it is recommended that the lowest dose with the smallest number of injections per site be used for TN management and injections be repeated only when pain returns and not at the perceived endpoint of BoNT efficacy. According to existing data, 25–40 U BoNT administered intra-dermally/mucosally into 15–20 sites (2–2.5 U/point) is recommended for TN therapy [88]. Large well-designed, double-blind, placebo-controlled clinical trials with long follow-up periods are needed to determine the optimum treatment method and the efficacy, safety, and tolerability of the less used injection techniques. Pharmaceutical engineering to design target-specific BoNTs focusing on pain neurotransmission could be an interesting subject for future research.

Other Trigeminal Neuropathic Pains

In these types, the criteria of neuropathic pain are satisfied, and their major difference with TN is that the regions with allodynia are larger in the former compared to the punctate precipitation points of the latter.

Herpetic, Post-herpetic, Post-traumatic Trigeminal Neuropathic Pain and Other Disorders'

Definition, Classification, and Epidemiology

The herpetic and post-herpetic subtypes are recognized as pain on one side of the face in the area covering at least one of the trigeminal branches with a duration of more than 3 months and related to signs/symptoms of acute herpes zoster ("herpetic') in the same region as the pain or temporal relation to the acute infection

("post-herpetic"). Confirmation by PCR (virus in CSF or its DNA in the base of the eruption) or direct immunofluorescence assay (VZV antigen) of the original infection is required [9]. Post-herpetic neuralgia is more common in men and has an overall estimated incidence of 3.9–42.0/100,000 person per year, which increases with age. In the trigeminal region, it affects the ophthalmic nerve more often, but its specific incidence is not known and has been reported to be the second most common site of reactivation after the thoracic dorsal root ganglion [7, 9, 89, 90].

Post-traumatic trigeminal neuropathic pain (PTTNP) develops within 6 months after any kind of trauma to the peripheral trigeminal nerve(s) and leads to persisting or recurring pain in one or both sides of the face or oral cavity (>3 months), with or without other signs of nerve dysfunction. The pain should be accountable by detecting a lesion of the nerve(s) by acceptable diagnostic tests, and somatosensory symptoms may be positive or negative. Dental interventions constitute an important cause of injury and can be caused by injections, endodontic therapy, tooth extractions, and surgical procedures, including implant placement [9]. The incidence of this type of pain is extremely difficult to assess, since there is a large individual variability following similar injuries and different procedures have different odds of causing PTTNP, which have been reported to range from 0.3% to 13% [1, 91].

Management of Herpetic, Post-herpetic, Post-traumatic Trigeminal Neuropathic Pain and Other Disorders

Due to the lack of large studies with adequate treatment duration and follow-up periods, an exact management protocol for post-herpetic trigeminal neuropathic pain does not exist, and the evidence is generally insufficient. The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG) has recommended antidepressant, anticonvulsant, and anxiolytic medication as first line of therapy, 5% lidocaine and 8% capsaicin patches and tramadol as second-line therapy, and BoNT and opioids as third-line therapy [90].

For PTTNP, there is no consensus on the best timing and treatment modality, and most approaches have not rendered favorable results, especially considering the low drug response rate (11%) of PTTNP compared to other neuropathic pain entities (20–40%). Therefore, management of these patients mostly involves improving quality of life through coping strategies and minimizing pain and functional impairments [92, 93].

Efficacy of BoNT in the Treatment of Post-herpetic Trigeminal Neuralgia

BoNT administration can be a helpful option for the management of post-herpetic neuralgia, considering that the disorder arises more commonly in older people who have underlying comorbidities that limit certain strategies. According to Safarpour and Jabbari [88] and based on two AAN class I studies, there is Level A evidence for the efficacy of BoNT therapy in post-herpetic neuralgia. However, the information on the treatment outcome of this toxin in trigeminal nerve involvement is insufficient. The importance of this issue is that studies have shown that trigeminal

herpes could be more painful than involvement of other nerves [94] and has been known to respond less to treatments and be more difficult to manage [95, 96]. It has been suggested that trials on treatment strategies for post-herpetic neuralgia should analyze different locations, separately [97].

In a prospective, randomized, placebo-controlled, double-blind, parallel group study, 60 participants were allocated into placebo, lidocaine, and BoNT (BTX-A, Lanzhou, China) groups (20 patients per group). Subcutaneous injections of BTX-A were given 1–2 cm apart, and depending on the painful area, patients received up to 200 U of the toxin. Improvements in pain intensity (visual analogue scale, VAS), sleep time (hours), and the reduced need for opioid use were significantly greater in the BoNT group compared to each of the other groups. Post-herpetic neuralgia was located in the orofacial region in 11 of the patients, but no further information was provided on them, except that they experienced more pain during the injections [98].

Another study reported significant pain relief within 16 weeks in 19 post-herpetic pain patients following administration of 500 U BoNT (Dysport) in 25 points. Three of them had ophthalmic involvement, and the authors stated that pain reduction was not associated with "dermatomal involvement" [99].

In an observation of eight cases with intractable post-herpetic neuralgia, the trigeminal nerve was involved in six out of eight patients (V1 and V2). The thoracic region was the site of involvement in the other two cases. A total dose of 50–100 U BoNT (Botox) was injected intradermally at multiple sites 2 cm apart, which showed significant pain relief in five out of eight subjects, starting from day 7 and continuing to approximately 74 days post-injection. Further information on the involved nerve of the five patients who demonstrated pain relief was not provided [100].

Comments

It is not yet clear whether post-herpetic neuralgia originating from the trigeminal nerve responds differently to BoNT therapy as compared to other nerves involved by this disorder. The preliminary data demonstrates that BoNT-A relieves pain in some patients with recalcitrant post-herpetic pain in the trigeminal distribution. To elucidate this issue, further studies, preferably controlled clinical trials, are needed to determine whether there is a need to modify the existing BoNT injection technique for patients with post-herpetic trigeminal neuropathy.

Efficacy of BoNT in the Treatment of Post-traumatic Trigeminal Neuropathic Pain

There is Level A evidence, based on two AAN class I studies, confirming the effectiveness of BoNT treatment in post-traumatic neuralgia, none of which included PTTNP cases [88]. It has been suggested that PTTNP is more challenging to manage than other neuropathic pain disorders like spinal traumatic neuropathies, due to possible differences in pathophysiological mechanisms [101].

In order to gather and present data on BoNT effectiveness in post-traumatic neuralgia affecting the trigeminal nerve and the orofacial region, a literature search using Medline and Google Scholar showed significant variability in the descriptive nomenclature and considerable overlap in the classifications. "Atypical odontalgia" has been considered a subtype of persistent idiopathic facial pain (PIFP) by ICHD-3; however, at the same time, when associated with a history of trauma, the ICHD-3 states that it could also be classified as a subtype of PTTNP but declares insufficient data to suggest definitive diagnostic criteria. Furthermore, according to ICHD-3, "A continuum seems to exist from *Persistent idiopathic facial pain* induced by insignificant trauma to *Painful post-traumatic trigeminal neuropathy* caused obviously by a significant insult to the peripheral nerves" [102]. ICOP suggests diagnostic tests and other criteria that may be helpful to differentiate these disorders [9]. However, considering the limited number of reported cases in the literature in addition to different descriptive terms and inadequate information in the existing reports (especially those that are older), it was not possible to accurately differentiate between these two entities. Therefore, we have divided all studies on PTTNP, dentoalveolar neuropathic pain, atypical odontalgia, persistent idiopathic dental/facial neuralgia, and similar terms into two lagre groups: those that have a documented history of any kind of trauma and are suggestive of PTTNP (Table 16.5) and those with no evidence of any traumatic event that would be suggestive of persistent idiopathic facial/dentoalveolar pain (Table 16.6, also see sections "Persistent Idiopathic Facial Pain (PIFP)" and "Persistent Idiopathic Dentoalveolar Pain (PIDP)").

Table 16.5 summarizes the reports of BoNT treatment in patients with *trigeminal neuropathic pain with a history of trauma/dentomaxillofacial procedure (suggestive of PTTNP)* [103–110]. In these cases, applied BoNT doses ranged between 10 U and 250 U, but achievement of pain relief was satisfactory in most subjects. The available information indicated between four and ten injection points that were divided among the painful regions to fulfill the predetermined total doses. Different BoNT types such as onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and South Korean type A toxin (Meditoxin and Innotox) were used in these studies. Intraoral administration sites were more common in the facial gingiva and vestibular mucosa, but tooth socket, hard palate, and labial mucosa were also injected. Extraoral administrations included intradermal and intramuscular routes. Effects were reported as early as 3 days and as late as 1 month, lasting between 2 and 5 months. No serious long-term adverse events were observed in these cases. Of the 18 subjects reported in Table 16.5, there were a total of three female nonresponders [107, 109]. Two of them had a history of orthognathic surgery (20 U) and extraction of tooth #30 (10 U). The authors suggested the possibility that further repeat cycles might have achieved significant results in these patients [109]. The other subject, a 52-year-old female, was reported as having persistent idiopathic facial pain, but considering the history of endodontic therapy, we included her in this section. The time of initiation of the pain after her dental treatment was not stated. Following endodontic treatment of the mandibular left first molar and first premolar, pain developed in the left lower "hemiface" and gradually intensified and was referred to the maxillary left quadrant. During the next 5 years, she received a series of

Table 16.5 Studies on the use of botulinum neurotoxin for management of trigeminal neuropathic pain in patients with any history of trauma or dentomaxillofacial procedures, suggestive of post-traumatic trigeminal neuropathic pain

Author/year	Study type	Patients	Chief complaint	History of trauma/ procedure	BoNT	Dosage	Injection	Assessments	BoNT Outcome
Yoon et al. 2010 [103]	Case report	Female 62 y	"Electric-like discomfort" + numbness in left lower lip and chin exacerbated by washing, touching, cold	Four implants (#22, #24, #25, #27) 2 m earlier	Botox	10U	Middle chin (subcutaneous)	CST → reduced sensation in left lower lip and chin; CPT with a Neurometer®	CPT → change from 1st m, sustained to 2nd m Patient noticed reduced area at 1st m and slight pain decrease at 2nd m
Cuadrado et al. 2016 [104][a]	Clinical study	Male 31 y	Moderate to severe stabbing/ piercing pain in left max dental arch and missing molar + spread to left mand arch and hard palate	Endodontic surgery of #14 and extraction	BOTOX®	10 × 2.5U Total: 25U	Tooth socket (*N* = 1), left max (*N* = 3), and mand (*N* = 3) gingiva (facial papillae at pain area) and hard palate (*N* = 3)	Dental exam → no clinical, XRay or CT pathology; Blood tests including ESR → normal	Pain relief from 3rd d lasting to 4 m; almost complete relief after five cycles
Herrero Babiloni et al. 2016 [105]	Case report	Female 60 y	7 y deep-tissue constant ache in right V2 andV3 with 5–10 sharp episodes/d	Endodontic treatment of #29	BOTOX® with 2% lidocaine as solvent	6 × 17U Total: 102U	Posterior vestibular sulcus of right max molar region (*N* = 3) and attached gingiva around #29, (*N* = 2 buccal + 1 ling)	MRI → negative, NRS (pain), – Nasopalatine & local #29 block reduced pain	Pain relief from 1–2 w lasted to 2 m

García-Sáez et al. 2018 [110][b]	Quasi-experimental, prospective, open-label, non-controlled study	Male: 51 y	Pressing pain in missing #17 area and left lower lip with spread to left lower dental arch	Extraction of #17	Botox	8 × 2.5U Total: 20U	Left mand gingival facial papillae (*N* = 6) and left side of the lower lip (*N* = 2)	NRS (pain) Response rate: proportion of patients > 50% pain reduction	Pain relief from 14th d lasted to 4–5 m
		Female 48 y	Pressing pain in left max dental arch & missing molars with spread to left side of upper lip	Extraction of #14, #15, #16	Botox	8 × 2.5U Total: 20U	Left max gingival facial papillae (*N* = 6) and left side of the upper lip (*N* = 2)		Pain relief from 7thd lasted to 3 m
		Female 42 y	Throbbing pain in missing molar	Extraction of #18	Botox	4 × 2.5U Total: 10U	Left lower gingival facial papillae (*N* = 4)		Pain relief from 2nd d lasted to 3 m
		Female 77 y	Dull pain in missing molar with spread to left mand dental arch	Extraction of #19	Botox	6 × 2.5U Total: 15U	Left lower gingival facial papillae (*N* = 6)		Pain relief from 7th d lasted to 3 m
Borges et al. 2018 [107][c]	Case report	Female 52 y	Diffuse, pulsatile, shocking, low frequency/intensity pain in left mand hemiface, with referral to ipsilateral max with time Crises ➞ pulsatile, burning + allodynia and irradiation to the superior alveolar branch region	Endodontic treatment of #21 and #19, 5 y earlier, after which pain started and got worse	BoNT-A	Total: 200IU	NS	Continuous visual scale, DN4 ➞ positive for neuropathic, DSM-5, LSSI, SF-36, HADS, PSQI-BR	No improvement after BoNT injection

(continued)

Table 16.5 (continued)

Author/year	Study type	Patients	Chief complaint	History of trauma/ procedure	BoNT	Dosage	Injection	Assessments	BoNT Outcome
Kim et al. 2018 [108]	Retro-spective case series	Female 67 y	Pain in max left ant buccal vestibule+tightening of upper lip	Multiple maxillary dental implants	Dysport	Total: 250U	Upper part of mucosa	NS	Second injection of 250U was given 3 months later and the pain did not recur
		Female 52 y	Pain in left side of face, masseter, zygoma and TMJ area + left cheek excessive salivation	Facial nerve reconstruction during plastic surgery	Innotox	Total: 25U	Left masseter	NS	Pain reduced 2 w later but still present 2nd course started 6 m later, still had some pain 3rd course given 3 m later, pain was tolerable
		Female 62 y	Pain in right lower lip and chin	Exact source of trauma not specified	Meditoxin	Total: 100U	Intraoral	NS	Pain was relieved and 2nd course was given
		Female 71 y	Pain in left face, lip gingiva	Exact source of trauma not specified	Innotox	Total: 20U	Intraoral	NS	Pain relief
		Female 68 y	Facial pain	Exact source of trauma not specified	Dysport	Total: 250U	Temporalis	NS	Pain relief

Moreno-Hay et al. 2018 [109]	Case series	Male 73 y	Pain in left mand lateral incisor	Dental treatment #23	Botox	Total: 20U	Vestibular mucosa or attached gingiva, doses divided among three evenly distributed sites	VRS (pain)	Pain reduction >50%, from 7th d, lasting 5 w
		Female 63 y	Pain in max central incisors	Dental treatment #9	Botox	Total: 10U			Pain reduction >50%, from 12th d, lasting 6 w
		Female 21 y	Pain in mand central incisors	Orthognathic surgery	Botox	Total: 20U			No response
		Female 49 y	Pain in right mand premolar and 1st molar	Extraction #30	Botox	Total: 10U			No response
De la Torre Canales et al. 2020 [106]	Case report	Male 44 y	8 y pain in left mand molar area, exacerbated by eating, brushing, etc.	Extraction of #19, pain followed 4 m later	Botox	10 × 5U Total: 50U	Buccal gingiva apical to #19, extended over #18 and #20	VAS, QualST (↑ hypersensitive to touch and pinprick), PGIC, Inferior alveolar block reduced pain	Pain relief from 2nd w to 5th m; recurred at 6th m

AE adverse events, *ant* anterior, *BoNT* botulinum neurotoxin, *d* day, *CPT* current perception threshold, *CST* Clinical Sensory Test, *DN4* Douleur Neuropathique en 4, *DSM-5* Diagnostic and Statistical Manual of Mental Disorders, *HADS* Hospital Anxiety and Depression Scale, *ling* lingual, *LSSI* Lipp's stress symptoms inventory, *m* month, *Mand* mandible, *Max* maxilla, *NRS* numeric rating scale, *NS* not specified, *PGIC* Patients Global Impression of Change, *PSQI-BR* Pittsburgh Sleep Quality Index, *QualST* qualitative sensory tests, *SF12* 12-item short form questionnaire, *SF36* short form (36), *TMJ* temporomandibular joint, *VAS* visual analog scale, *VRS* Verbal Rating Scale (0–10), *w* week

[a] This was an open, noncontrolled clinical study with four patients, one of which had a history of a traumatic event, hence his inclusion in this Table. Please see Table 16.6 for information on other patients

[b] This study reported a total of nine patients, four of which were presented previously by the same authors in the study by Cuadrado et al. (second row). All patients of both studies are being reported in Tables 16.5 and 16.6

[c] This case has been reported as persistent idiopathic facial pain (exact duration of onset after endodontic treatment has not been stated). It is being included here only due to the history of endodontic treatment

Table 16.6 Studies using botulinum neurotoxin for management of trigeminal neuropathic pain in patients with no history of trauma or dentomaxillofacial procedures suggestive of persistent idiopathic facial/dentoalveolar pain

Author/ year	Study type	Patients	Chief complaint	BoNT	Dosage	Injection	Assessment	Outcome
Cuadrado et al. 2016 [104][a]	Clinical study	Female 72 y	Moderate, burning pain in paramedian max and mand dental arches with spread to upper lip	Botox	12 × 2.5U Total: 30U	Max gingiva (*N* = 4), mand gingival facial papillae (*N* = 4) and upper lip (*N* = 4)	Dental exam → no clinical, XRay or CT pathology; Blood tests including ESR → normal results	Pain relief from 10th d lasted to 3 m; complete relief after three cycles
		Female 52 y	Mild to severe, stabbing/burning pain in left mand paramedian dental arch with spread to chin	Botox	8 × 2.5U Total: 20U	Paramedian and left mand gingival facial papillae		Pain relief from 14th d lasted to 3/6 m; almost complete relief after two cycles
		Male 53 y	Mild to severe, stabbing/burning pain in right max dental arch with spread to preauricular area	Botox	6 × 2.5U Total: 15U	Max right gingival facial papillae		Pain relief from 7th d lasted to 2 m almost complete relief after two cycles
Kim et al. 2018 [108]	Retrospective case series	Female 70 y	Pain in right max ant gingiva	Meditoxin	Total: 120U	Intraoral	NS	Not effective
		Female 66 y	Pain in left max posterior gingiva	Dysport	Total: 20U	Intraoral	NS	Not effective
García-Sáez et al. 2018 [110][b]	Quasi-experimental, prospective, open-label, noncontrolled study	Male: 46 y	Electric, continuous pain in right mand dental arch with spread to ipsilateral mand angle	Botox	6 × 2.5U Total: 15U	Right mand gingival facial papillae	NRS (pain): Response rate: proportion of patients > 50% pain reduction	Pain relief from 15th d lasted to 3–6 m

Moreno-Hay, 2019 [109]	Case series	Female 53 y	Pain in left max 3rd molar	Botox	Total: 20U	Vestibular mucosa or attached gingiva, doses divided among three evenly distributed sites	VRS (pain)	No response
		Female 66 y	Pain in right max premolar/lateral incisor	Botox	Total: 25U			Pain reduction >50%, from 12th d, lasting 1 w
		Female 43 y	Pain in left mand 2nd premolar/molar	Botox	Total: 10U			Pain reduction (25%), from 14th d, lasting 8 w
		Female 51 y	Pain in left mand canine/incisors	Botox	Total: 10U			Pain reduction (40%), from 15th d, lasting 5 w

AE adverse events, *ant* anterior, *BoNT* botulinum neurotoxin, *d* day, *m* month, *Mand* mandible, *Max* maxilla, *NRS* numeric rating scale, *NS* not specified, *VAS* visual analogue scale, *VRS* Verbal Rating Scale (0–10), *w* week

[a] This was an open, noncontrolled clinical study with four patients, one of which had a history of a traumatic event. Please see Table 16.5 for information on that patient

[b]This study reported a total of nine patients, four of which were presented previously by the same authors in the study by Cuadrado et al. (first row). All patients of both studies are being reported in Tables 16.5 and 16.6

diagnoses and treatments with no relief. Despite administration of one of the highest BoNT doses found among the current reports (200 U), the subject's pain did not subside. Pain from pulp conditions and posterior teeth can be referred to the ipsilateral opposite jaw [111]. Additionally, persistent ectopic pain can develop following trauma to the mandibular nerve fibers and eventually disseminate to regions innervated by other untraumatized trigeminal nerve branches [112]. Based on the provided information, it is not clear whether the pain in this patient originated from her endodontic procedure but maybe the referral nature of the pain made BoNT treatment less effective. Similar observations regarding the reduced efficacy of BoNT on referred myofascial pain were discussed above under treatment of TMD pain.

Intraoral injections are mostly safe and used routinely in dental practice. However, it has been suggested to be cautious during intraoral injection of BoNT by reducing the dosage and number of injections as much as possible but enough to achieve the desired effect [105].

Comments

Despite the encouraging results on BoNT efficacy in the treatment of *trigeminal neuropathic pain with a history of trauma (suggestive of PTTNP)*, drawing definitive conclusions on dosage and number of injection sites to use as a guideline is not possible at this point due to the limited number of available studies. Controlled and blinded studies are needed to define the efficacy of BoNT treatment in PTTNP.

Idiopathic Orofacial Pain

Idiopathic orofacial pain is defined as persistent, poorly localized pain of unknown cause with moderate intensity occurring on one or both sides of the face or oral cavity in the distribution area of ≥1 of the trigeminal branches identified as "burning," "pressing," or "dull" [9].

Persistent Idiopathic Facial Pain (PIFP)

Persistent Idiopathic Dentoalveolar Pain (PIDP)

These disorders have been classified as a single entity in ICHD-3 but are considered separately in ICOP [9, 102]. Based on the existing literature on BoNT, they will be considered together for convenience.

Definition, Classification, and Epidemiology

Persistent pain in the face not following a peripheral nerve distribution or occurring unilaterally in the dentoalveolar complex localized to a tooth or alveolar bone rarely in more than one site, recurring for >2 h/day for >3 months, with no detectable clinical, radiographic, or local cause, is regarded as PIFP and PIDP, respectively [9]. The further classifications of these entities are beyond the scope of this discussion. Considering the different classifications, terminology, and diagnostic criteria, an exact estimate of its prevalence is difficult to obtain, and ranges between 0.03% and 1% have been reported with a higher incidence in 40- to 50-year-old females [1, 113].

Management of Persistent Idiopathic Facial and Dentoalveolar Pain

Due to the ambiguous nature of these disorders, a specific treatment has not been developed, and the level of evidence for the suggested therapies, like low-level laser, tricyclic antidepressants, duloxetine, venlafaxine, and anticonvulsants, is low [1].

Efficacy of BoNT in the Treatment of Persistent Idiopathic Facial and Dentoalveolar Pain

The number of investigations on BoNT effectiveness in PIFP and PIDP is scarce, and there are no placebo-controlled, blinded clinical trials. The studies are limited to case reports, case series, and open-label trials. Additionally, as stated above, due to overlaps in definition with PTTNP and lack of detailed data on patient characteristics in the existing reports, it would be difficult to collectively evaluate BoNT studies on PIFP/PIDP management. Table 16.6 illustrates cases of BoNT therapy in patients with *trigeminal neuropathic pain without a history of trauma/dentomaxillofacial procedures (suggestive of PIFP/PIDP)*. There were a total of ten cases reported in four studies [104, 108–110] that used 10 U–30 U BOTOX®, Meditoxin, or Dysport to inject into 6–12 points distributed in the gingiva. Of the treated cases, three patients did not respond, and two patients had less than 50% pain reduction, meaning that suboptimal results were obtained in 50% of patients.

Comment

With the small number of cases and lack of double-blind comparisons with placebo, the efficacy of BoNT in the treatment of *trigeminal neuropathic pain without a history of trauma/dentomaxillofacial procedure (suggestive of PIFP/PIDP)* is unclear at this stage, but it seems that the responsiveness of patients to toxin administration is not as favorable as the other neuropathic pain subgroups.

Burning Mouth Syndrome

Definition, Classification, and Epidemiology

ICOP describes BMS as a burning or dysesthetic feeling lacking an apparent local or systemic cause that occurs >2 h/day for over 3 months ("probable BMS" if less than 3 months). In addition, the pain has to be "burning" and "superficial" for diagnosis. This disorder is further divided into BMS with and without somatosensory changes, based on the results of quantitative sensory testing [9].

The global prevalence of BMS is 1.73% worldwide and 7.72% in dental clinics, with a higher prevalence in Europe (5.58%) and North America (1.10%) compared to Asia (1.05%). It occurs almost three times more often in women and is more prevalent in individuals >50 years of age [114].

There has been controversy regarding different aspects of this entity including nomenclature (replacing BMS with BM "disorder"), research diagnostic criteria, duration of symptoms, and pathophysiology [115, 116]. An important question that can influence treatment options is whether this disease is a neuropathic pain disorder, with some classification systems considering it as such [1, 7, 117]. Central and peripheral neuropathies have both been variably implicated in BMS. The former is associated with disruption of the dopaminergic or serotoninergic systems, while the latter involves peripheral neuropathy of the small-diameter fibers in the oral mucosa [117]. ICOP has also suggested the possibility of BMS being considered as a neuropathic pain condition [9].

Management of Burning Mouth Syndrome

There is no uniform evidence-based treatment strategy for BMS, but the most important initiative would be a correct diagnosis and ruling out all other entities with similar symptoms. Starting from the most conservative options like masticatory muscle exercise and hot pack, ultrasound and physical therapy are recommended. Pharmacotherapy with systemic or local agents like antidepressants, gabapentin, clonazepam, lycopene, lafutidine, and capsaicin and psychological treatments have been administered in these patients with variable results [6].

Efficacy of BoNT in the Treatment of Burning Mouth Syndrome

The number of studies on BoNT injection in BMS patients is scarce (Table 16.7), and the information provided on diagnostic criteria and treatment is insufficient [118–120]. The dosage used for effective management has ranged from 50 to 100 U, which was injected into masticatory muscles, the tongue, and lip, with effects starting from 48 hto 3 weeks later and lasting up to 20 weeks with no significant side effects.

Table 16.7 Outline of studies using botulinum neurotoxin for the management of burning mouth syndrome

Authors	Patients	History	Symptoms	BoNT	Dose	Injection site	Outcome	Time to effect	Lasting effect
Seo et al. 2009 [118]	*N* = 1 Female 54 y	Neuroleptic therapy	Tongue dyskinesia + severe oral burning 5 y after therapy for neuroleptic therapy	BoNT-A	50U	Tongue muscles	Both issues improved	10 d	NS, injections given each month for 2 y
Restivo et al. 2017 [119]	*N* = 6 Females: 5[a] Male: 1 67–76 y	Diabetes in 3 patients	Anterior 2/3 of tongue + lower lip for at least 6 m	Inco-botulinumtoxinA	16U	Bilateral lower lip + bilateral anterolateral tongue	Initial 60–90 VAS reduced to 0	48h	12–20 w
Kwon and Park 2020 [120]	*N* = 1 Female 60 y	N/S	Burning + dryness	Meditoxin	100U	60U in both masseters + 40U in both temporalis	Initial 5 NRS reduced to 2	3 w	N/S

d day, *h* hour, *NRS* numeric rating scale, *NS* not specified, *VAS* visual analog scale, *w* week, *y* year

[a] Two females initially received saline as placebo with no improvement after 4 weeks

The logic behind using this toxin relies on both its muscle relaxant and antinociceptive effects. Musculoskeletal issues and tension of the lingual muscles have been proposed as possible triggering factors for tongue pain [121, 122]. Parafunctional habits and masticatory muscle tenderness upon palpation are relatively common among BMS patients. Hypotheses like habit-induced microtrauma causing neuropathic alterations in the tongue and lingual nerve compression due to entrapment in the lateral pterygoid muscle have been suggested for the possibility of musculoskeletal involvement in BMS [120, 123].

As for the justification of the antinociceptive effect of BoNT in BMS, it should be noted that BoNT-A inhibits the activity and membrane translocation of transient receptor potential vanilloid-1 (TRPV1), and its effect has been shown in several pain models [124]. In BMS, there is a reduction of C-fibers in the lingual mucosa causing upregulation of TRPV1 (among other factors) in the remaining fibers, each responding to specific stimulations [117].

Comment

Based on the extremely limited number of reports on the use of BoNT for managing BMS, it is not possible to form a definitive opinion on its efficacy. However, considering the refractory nature of the disease, the favorable reports, and the safety of BoNT, it seems that this toxin may be a potential option for BMS treatment and warrants further investigation.

Case Report: Courtesy of B. Jabbari, MD [75]

A healthy 60-year-old man presented with significant painful hypersensitivity to touch on the gingiva adjacent to an extraction site with three missing left molars. The allodynia developed 3 years ago following the extractions and was described as attacks of severe and jabbing pain that radiated to the upper lip on the same side. The paroxysms occurred several times a day with an intensity of 9 or 10 on VAS and prevented him from comfortable brushing. He was currently on 600 mg gabapentin, q.i.d. which was not effective, similar to his past analgesic medications.

The allodynia on the gingiva, over and anterior to the extraction site, was confirmed on examination (Fig. 16.1), and he was injected intramucosally with 10 U (2.5 U × 4 points) of onaA in the painful area, 2–3 mm below the surface. Based on the preceding discussion, the pain could be classified as trigeminal neuropathic pain with a history of dentomaxillofacial procedure (suggestive of PTTNP). He reported distinct improvement of pain and discontinuation of the paroxysms after 7 days. The effects lasted up to 6 months, and a second round of treatment was administered at the patient's request, which yielded the same efficacy. He recorded a "very much improved" answer in PGIC (Fig. 16.1).

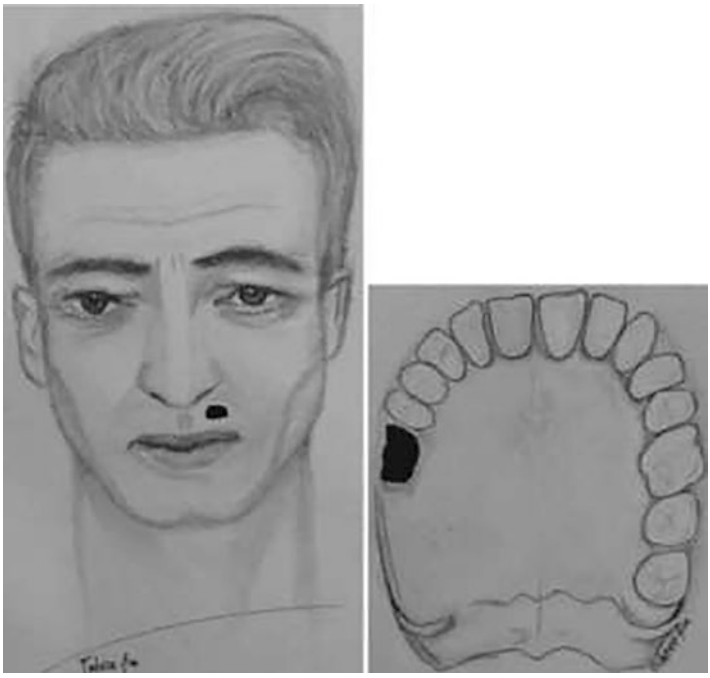

Fig. 16.1 Regions of allodynia on the gingiva covering an extraction site, with radiation to the upper lip on the same side. A total of 10 U (4 × 2.5 U) onaA was administered into areas demarcated with black ink. (Drawing courtesy of Damoun Safarpour, MD)

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