Topical Review: Potential Use of Botulinum Toxin in the Management of Painful Posttraumatic Trigeminal Neuropathy

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Painful posttraumatic trigeminal neuropathy (PPTTN) is a chronic condition that is difficult to endure and has a poorly understood pathophysiology. Treatment options are limited and often unsatisfactory due to insufficient efficacy and significant adverse effects. Botulinum toxin type A (BTX-A), initially used in the management of pathologically sustained or twisting muscular contractions, has recently been advocated for treatment of neuropathic pain. Its action is not limited to the blockage of acetylcholine release at the neuromuscular junction, but also includes inhibition of exocytosis of other neurotransmitters by interfering with the SNARE complexes of synaptic membranes. When injected into the painful location, the toxin can be taken up by peripheral terminals of nociceptive afferent nerve fibers, and this action suppresses peripheral and central release of algogenic neurotransmitters such as glutamate or substance P, thus promoting analgesia. Several randomized controlled trials in humans have provided emerging evidence for the therapeutic use of BTX-A in neuropathic pain states, including trigeminal neuralgia. This evidence, in addition to its good safety profile and long-lasting effect, suggests that BTX-A could be a potential novel treatment for PPTTN. *J Oral Facial Pain Headache 2017;31:7–18. doi: 10.11607/ofph.1753*

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Traumas of either physical (eg, shocks, ballistic impacts) or surgical origin are accompanied by acute pain, which usually dissipates with physiologic tissue healing. However, in some instances, in spite of apparent normal tissue repair, pain may persist as a result of peripheral and central alterations in neuronal function. The impact of such neuropathic pain is important as it affects individual quality of life and hedonic, emotional, social, and professional dimensions of life and poses a considerable economic burden to society (eg, treatment costs, work absenteeism, loss of motivation and concentration, etc).[1,2] Among these painful conditions, painful posttraumatic trigeminal neuropathy (PPTTN) resulting from orofacial nerve damage following physical or surgical trauma has received limited study. It should be noted that similar, or at least partially overlapping, chronic orofacial pain entities might have received different names throughout the scientific literature,[3,4] including phantom tooth pain,[5] atypical odontalgia/atypical facial pain,[6–8] persistent dentoalveolar pain,[9] peripheral painful traumatic trigeminal neuropathy,[10] or persistent idiopathic orofacial pain,[8] thus complicating the undertaking of systematic reviews on PPTTN. Few studies in the orofacial area have indeed adopted the stringent and operationalized criteria established for neuropathic pain.

The available studies suggest a high prevalence of PPTTN that ranges from 0.5% to 12% following endodontic treatment, simple or complex teeth extractions (such as wisdom teeth extraction), dental implant placement, and other surgical procedures (eg, cyst removal, orthognathic surgery).[11] However, despite recent significant advances, the pathophysiologic mechanisms underlying this painful condition are still largely unknown. The majority of PPTTN cases are clinically resistant

to standard analgesics and are thus extremely difficult to manage.[11–13] Therefore, finding new therapeutic solutions for such conditions is of major clinical significance for the oral medicine and orofacial pain specialist.

The aim of this article is to review current evidence regarding the use of botulinum toxin (BTX) as an analgesic in neuropathic pain conditions and its potential use for PPTTN management. As idiopathic trigeminal neuralgia involves the same region and is also of a neuropathic nature,[14] clinical data pertaining to the use of BTX in this condition will also be included in this review as indirect evidence supporting its use in PPTTN.

Clinical Presentation and Pathophysiology

Patients suffering from PPTTN typically complain of constant moderate to severe pain of burning quality.[11] However, many variants can be observed regarding pain quality and time course. Typically, pain can be described as pricking or stabbing, and paroxysmal pain attacks more typical of idiopathic trigeminal neuralgia can also occur, although with different patterns. Pain in PPTTN is unilateral in 90% to 95% of cases,[10,15] with a possible bilateral presentation. Bilateral presentations occur especially following important traumas (bilateral pain in 7% of cases following dental trauma vs 18% following macrotraumas[10]) located along the territory of the injured nerve branch, but may spread to several other nerve branches. Patients may also complain of a feeling of swelling, foreign body, hot or cold, or local redness or flushing; for example, in a study of 91 PPTTN cases,[10] 10% of patients presented with redness and swelling, and perceptual distortion has been reported in more than 80% of PPTTN patients in another study.[16] Nonpainful but annoying dysesthesias such as itching or numbness are often also present. Local somatosensory dysfunctions can be evidenced by quantitative sensory testing.[17]

The temporal characteristics of PPTTN have been poorly documented; the pain may persist for months or years.[4] In a retrospective study, Peñarrocha et al found that 25% and 30% of cases achieved partial or full sensory recovery, respectively, at the 1-year follow-up posttrauma; however, the study was not limited to pain.[15] From a pathophysiologic point of view, the development of painful symptoms after peripheral nerve injury is related to peripheral and central changes. Damaged tissue byproducts initiate peripheral changes at the injury site that result in functional changes in neuronal, glial, and vascular cells, followed by ganglionic and central changes. These changes modify both the functioning and excitability of individual neurons and the configuration of synaptic networks at the spinal cord/brainstem and higher brain levels, eventually leading to genetic and epigenetic changes that translate as long-term alterations of neuronal phenotypes. Pathophysiologic processes related to PPTTN are noted below in the next section, but for more in-depth descriptions of pathophysiologic mechanisms, the reader is referred to recent comprehensive reviews.[18–25]

Management

Because of the low prevalence of PPTTN, the absence of objective biomarkers, the presence of comorbidities such as psychological distress or an anxio-depressive state, and the lack of knowledge that most practitioners have about PPTTN, the diagnosis of PPTTN is difficult, often leading to a variety of therapeutic approaches. During consultations (typically many; an average of 7.5 practitioners are consulted), patients usually receive different treatments such as surgical treatment, antidepressants, and analgesics or alternatives that are often ineffective and potentially iatrogenic. Additional psychotherapeutic intervention is often required.[12,26,27]

Surgical management of patients with PPTTN is controversial. Long-term results of micro-neurosurgical procedures are often anecdotal, variable, and operator dependent. In addition, these results are often difficult to assess, as such studies are rare and involve few patients. Thus, a thorough evaluation of these techniques is necessary before advocating any surgical treatment for PPTTN, and many authors recommend stopping any planned surgical procedures in the painful territory and contraindicate future surgery, as it might worsen the patient's pain.

Pharmacologic management of PPTTN, similar to that of posttraumatic spinal neuropathic pain, is mostly symptom based, combining systemic medication with topical ointments such as anesthetics and capsaicin. As for other types of neuropathic pain, PPTTN seldom responds, if at all, to classic analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), and is thus treated by other therapeutic classes. Current management is based on the recommendations of the European Federation of Neurological Societies (EFNS) and the American Pain Society (APS).[2,11,28] Pharmacologic management is dominated by the use of tricyclic antidepressants (amitriptyline or others), anticonvulsants (gabapentin, pregabalin, carbamazepine, clonazepam), opioids (morphine, tramadol), and inhibitors of the reuptake of serotonin and norepinephrine (venlafaxine, duloxetine). However, these types of medi-

cation present many contraindications and induce numerous adverse effects that are more or less tolerated, among which dizziness, dry mouth, and gastrointestinal disorders are the most frequent. For these reasons, patients sometimes abandon treatment or reduce their medication dosage, which results in impaired efficacy of the medication.

Interestingly, PPTTN seems more difficult to treat than other neuropathic pain conditions such as postherpetic neuralgia, painful diabetic neuropathy, and painful spinal traumatic neuropathies. In a series of 91 PPTTN cases, 11% of the patients had a ≥ 50% reduction in pain intensity (or 25% of patients when considering a ≥ 30% improvement) with pharmacologic treatment, whereas a 20% to 40% response rate has been reported in the other aforementioned conditions.[12]

Convergent behavioral, electrophysiologic, neuroanatomical, and pharmacologic data indicate that there may be significant differences between PPTTN and painful spinal posttraumatic neuropathies in their underlying pathophysiologic mechanisms.[11,29] The nature of sensory nerves (eg, the presence of autonomic fibers, percentage of myelinated fibers) more prone to damage, redundancy of somatic representation and functional organization, pattern of glial activation, and differential involvement of the various chemokines may explain such differences.[11,29]

In view of these difficulties in treatment, there is a need for alternative therapeutic modalities—preferably local intervention—that spares patients of more severe systemic undesirable side effects.[2]

Botulinum Toxin and Pain

Botulinum Toxin

Botulinum toxin (BTX), produced by *Clostridium botulinum*, is a polypeptide composed of a 100-kDa heavy chain linked to a 50-kDa light chain by a disulfide bridge (Fig 1). The heavy chain binds the toxin molecule to the neuronal receptor, thus allowing the translocation of the light chain, which is responsible for the toxin's enzymatic activity. This light chain is a protease that attacks the SNARE complexes within the neuromuscular junctions, preventing vesicular fusion with the cytoplasmic membrane and the release of their contents. BTX therefore affects vesicular release of neurotransmitters and neuromodulators.[30,31] One major effect of BTX is the blockage of the release of acetylcholine (ACh), thereby preventing muscular contraction; this explains the high lethality of the toxin since it can lead to asphyxia by diaphragmatic paralysis. There are seven known serotypes of BTX that share the same structure and molecular weight, among which botulinum toxin type A (BTX-A) has been the most studied for medical use. Therapeutic doses are expressed in units of biologic activity (Units [U]), one U corresponding to the median lethal dose (LD50) in intraperitoneally injected, 18–20-g female Swiss-Webster mice. In view of the relatively few studies on the use of botulinum toxin type B in the management of neuropathic pain and PPTTN, this article will focus on BTX-A only.

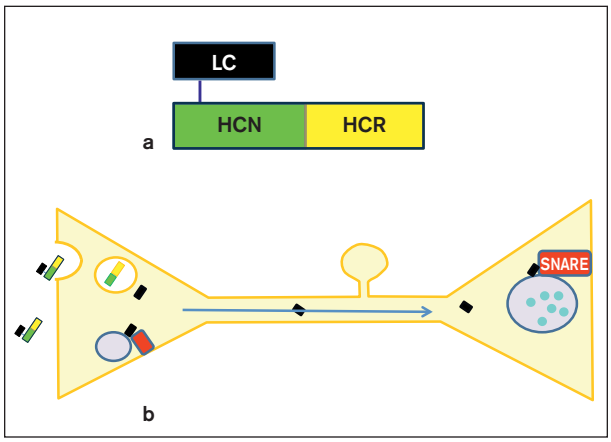

Fig 1 Structure and mode of action of the botulinum toxin (BTX). **(a)** BTX is composed of a heavy chain (HC) that is functionally divided into the receptor-binding domain (HCR) and the translocation domain (HCN) and is linked by a disulfide bridge to a light chain (LC), which is a protease. **(b)** The neurotoxin binds to the cell membrane, is internalized via endocytosis, and released into the cytosol where it interferes with the SNARE complex, either at the peripheral or central terminals (after retrograde transport [*arrow*]), eventually preventing the release of neurotransmitters.

Therapeutic Use of BTX-A

Since its introduction in the 1970s for the treatment of strabismus, blepharospasm, and focal dystonia, BTX-A has been widely used in the treatment of conditions characterized by excessive muscle contractions and/or involving the cholinergic system (eg, focal dystonia, spasticity, abnormal sphincter contractions, eye movement pathologies, and hyperkinetic and vegetative disorders). Many studies have also been conducted in cases of painful conditions involving a muscular component.[32] The neurotoxin has since been used in other types of painful disorders including myofascial pain, blepharospasm, myalgia of temporomandibular disorders, back pain, painful myoclonia, urologic, rectal, or pelvic pain, cervicogenic, neurovascular, and tension-type headaches, and migraine, with variable results depending on the condition and dose.[32] It is in the neuromuscular junction that the action of BTX has been the most studied. BTX-A blocks the release of ACh and causes a reversible denervation of the motor endplate (reversible

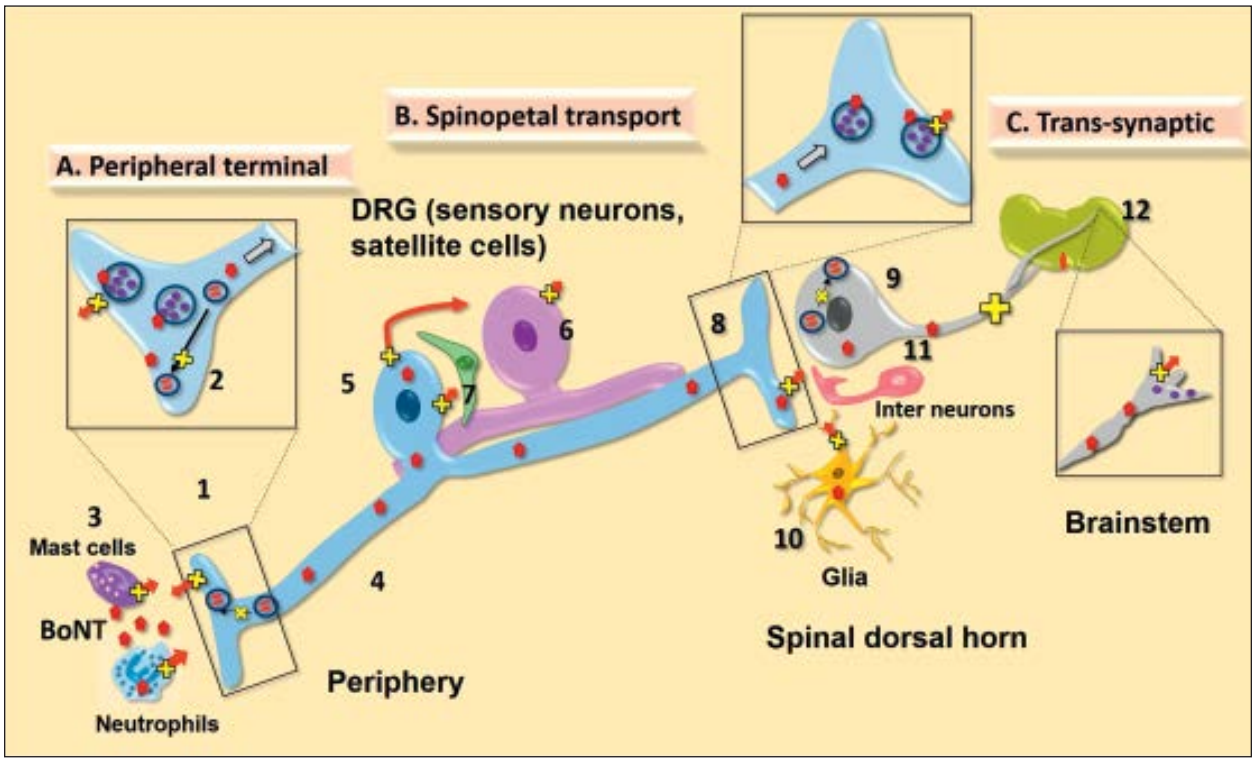

Fig 2 Schematic representation of possible mechanisms of action of peripherally applied botulinum neurotoxin (BoNT/A1 and /B1) on nociceptive processing. **(A)** Periphery. *(1)* At the site of injection, BoNTs are endocytosed into the local peripheral afferents, where BoNTs cleave SNAREs, thereby inhibiting vesicular fusion and neurotransmitter exocytosis. This in turn could block vasodilation, plasma extravasation, and activation of local inflammatory cells. *(2)* In this way, BoNTs may also regulate SNARE-mediated cell surface expression of a variety of receptors and channels implicated in peripheral sensitization (eg, TRPV1). *(3)* Another hypothesis is that BoNTs may enter local resident cells (eg, mast cells) or migrating cells (eg, neutrophils) evoked by injury or inflammation and may directly block the release of cytokines or proinflammatory molecules, both of which can activate and sensitize local small afferent terminals. **(B)** Spinopetal transport. *(4)* Following endocytosis in the peripheral terminals, some of the BoNTs appear to undergo retrograde transport along the axon. *(5)* These transported BoNTs reach the dorsal root ganglion (DRG) neurons and cleave SNAREs in the DRG neurons to block vesicular release of neurotransmitters into the extracellular milieu of the DRG, which would otherwise activate and *(6)* excite the neighboring sensory neurons or *(7)* closely associated satellite cells. *(8)* BoNTs may further undergo intravesicular axonal trafficking to the central terminals, where again, by truncating respective SNAREs, they could inhibit neurotransmitter release, thereby preventing the activation of second-order neurons and neighboring glial cells. **(C)** Transsynaptic actions. BoNTs can undergo axonal transport in intact form in nonacidic endosomes and may possibly undergo transcytosis centrally either to the *(9)* second-order neurons or *(10)* glial cells. Activated glial cells release a plethora of proalgesic substances (eg, cytokines, chemokines, lipids, amino acids) serving to initiate and maintain central sensitization. *(11)* BoNTs may also get transcytosed to excitatory (glutamatergic) inhibitory (GABA/glycinergic) interneurons and may act to block their neurotransmitter release, thus resulting in a loss of excitatory drive or inhibitory control, respectively. Cleaved SNAREs in the second-order neurons may interfere with fusion of endosomes that carry the receptors to the membrane. *(12)* Although speculative, if there is transcytosis to second-order projection neurons, it is a reasonable hypothesis that these BoNTs are transported to distal terminals in the brainstem and further block the neurotransmission into the brainstem and higher centers. *Adapted from Pellet et al[31] with permission.*

in 28 days). Recovery initially occurs by sprouting and the restoration of function in the initial innervation and loss of sprouts. Full recovery is achieved in about 90 days. However, this sole effect appears insufficient to explain all of the neurotoxin's analgesic activity, which has been demonstrated in numerous animal studies and therapeutic clinical trials.

Effects of BTX-A on the Nociceptive System

The analgesic effect of BTX-A may be related to a peripheral action by blockage of the axon reflex that normally results in the release of neuropeptides such as substance P (SP), neurokinin A (NKA), or calcitonin gene-related peptide (CGRP) by small-diameter type C primary afferent nerve fibers, generating neurogenic inflammation characterized by vasodilation and increased vascular permeability. BTX-A has been shown to inhibit the release of SP and glutamate[33] and to reduce the nociception induced by formalin injection.[34] In addition, the toxin can be taken up by nerve endings and transported by retrograde and orthograde axonal transport to remote sites, such as the primary afferents' level of termination,[35–37] or to other sites of neuronal interaction with glial or other neuronal cell types (Fig 2).[38,39] BTX-A can therefore inhibit the release of algogenic neurotransmitters present in

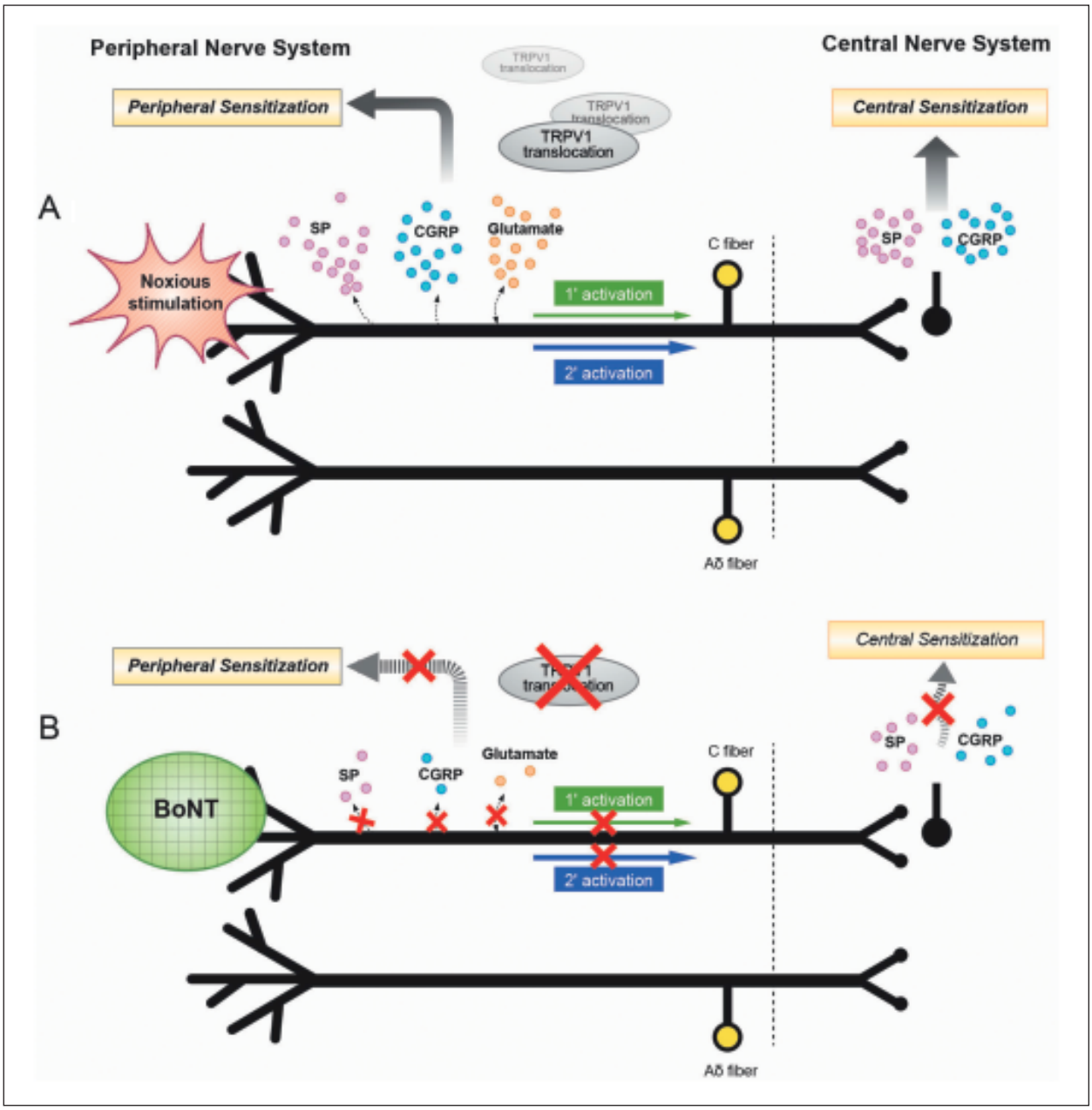

Fig 3 **(A)** Molecular mechanisms of peripheral and central sensitization. Noxious stimulation may lead to peripheral sensitization through the release of neuropeptides and inflammatory mediators. The peripheral sensitization may in turn result in sensitization of the central nervous system. SP = substance P; CGRP = calcitonin gene-related peptide; TRPV1 = transient receptor potential vanilloid 1. **(B)** The antinociceptive mechanism of botulinum neurotoxin (BoNT) in the treatment of neuropathic pain can be explained by a decrease in peripheral SP, CGRP, and glutamate release and TRPV1 receptor translocation, leading to the inhibition of peripheral sensitization. As SP and CGRP secretion are blocked within the central nervous system, central sensitization is also indirectly reduced. *Reproduced from Oh et al[91] with permission.*

nociceptive primary afferents (eg, neuropeptides SP and CGRP, glutamate) both peripherally and in the central nervous system (CNS) (Fig 3).[40] For example, in a Complete Freund's Adjuvant–induced inflammatory trigeminal model, pericranially injected BTX-A was taken up by local sensory nerve endings, axonally transported to the trigeminal ganglion, and transcytosed to dural afferents, where it prevented dural inflammation and CGRP increase.[41] Postsynaptic events preventing phosphorylation of a glutamate receptor (GluA1 subunit) and a kinase (Akt) might account for the prevention of central sensitization following BTX-A injections.[42] BTX-A also decreases the expression of transient receptor potential vanilloid 1 (TRPV1) receptors on the membrane surface of nociceptors in animals[43,44] and humans.[45] These receptors are involved in the transduction of thermal information and their activation results in a burning sensation, which

is a frequently reported qualitative pain characteristic in posttraumatic neuropathic pain. For instance, administration of BTX-A decreased the expression of TRPV1 in dorsal root ganglion neurons in a model of posttraumatic neuropathic pain.[46] Finally, the toxin can also decrease the expression of other nociceptive receptors such as purinergic receptors (P2X3).[47]

BTX-A could be of special interest for posttraumatic neuropathic pain. Some studies have investigated the effect of BTX-A in the sciatic nerve chronic constriction injury (SN-CCI) model of spinal posttraumatic neuropathic pain, and the results showed a decrease in thermal and mechanical allodynia following BTX-A injections.[48–50] Marinelli et al[51] further indicated that a single injection of BTX-A in CD-1 mice was sufficient not only to reduce allodynia and thermal and mechanical hyperalgesia, but also to improve the functional recovery of the injured paw and improve the regeneration of the injured nerve. Using other posttraumatic neuropathic pain models closer to PPTTN such as infraorbital nerve chronic constriction injury (IoN-CCI), several studies have shown a similar effect of local BTX-A injections on thermal and mechanical allodynia in the painful orofacial territory.[35,52–54] Administration of BTX-A also reduced the IoN-CCI–induced upregulation of nociceptive receptors TRPA1, TRPV1, and TRPV2 (but not TRPM8) in the spinal sensory complex.[55]

The use of this toxin thus seems promising for the management of neuropathic pain since intradermal injection of BTX-A in healthy volunteers resulted in a specific and marked decrease in painful mechanical sensitivity without any alterations in nonnociceptive (tactile) mechanoreception and without affecting cutaneous innervation density.[56]

Usefulness of BTX-A in Human Spinal and Trigeminal Neuropathies

Several human studies have assessed the effects of BTX-A in different types of neuropathic pain with pain as a primary outcome (other secondary outcomes being concomitant medications, sleep, quality of life, etc). In a study focusing on postsurgical pain, injections of BTX-A improved pain but the diagnosis of neuropathic pain was uncertain.[57] In a pilot study including five patients with neuropathic pain related to carpal tunnel syndrome, a trend toward improvement in visual analog scale (VAS) scores was observed at 3 months.[58] A preliminary report from a randomized controlled trial (RCT) conducted in painful diabetic neuropathy patients suggested that BTX-A injections resulted in improvement of pain as well as in other health variables.[59] In 23 patients with head and neck postsurgical neuropathic pain, pain and quality of life were significantly improved in the treatment group.[60] The first strong evidence supporting the use of BTX-A for neuropathic pain management came from a double-blind RCT that evaluated 29 patients with different types of focal neuropathic pain (postoperative, posttraumatic, or postherpetic).[61] Injections of BTX-A in the area of the pain resulted in statistically significant pain relief, over 50% reduction in pain at 3 months compared to placebo. In 18 patients with painful diabetic peripheral neuropathy, BTX-A significantly reduced pain intensity at 3 months and improved sleep quality.[62] It is noteworthy that, as observed in the study by Ranoux et al,[61] the alleviation of pain started after the first week. In a double-blind, single-dose, placebo-controlled RCT in 30 postherpetic neuropathic pain patients, BTX-A led to a 50% reduction in VAS scores in 85% of BTX-A patients, compared with no patients in the placebo group. The effect lasted for 4 months and a concomitant amelioration of sleep was noted.[63] In another study of 20 subjects with postherpetic neuropathic pain who were injected with BTX-A, VAS pain scores decreased at day 7 and at 3 months posttreatment significantly more than in the control groups (lidocaine and placebo); in addition, BTX-A improved sleep and reduced the use of opioids.[64] In patients with spinal cord injury, a double-blind RCT demonstrated a significant reduction in VAS pain scores at 1 and 2 months after BTX-A injections compared to placebo.[65] The effect was associated with slight improvement of physical health. In a recent multicentric double-blinded RCT in 66 patients with peripheral neuropathic pain, Attal et al[66] found a significant pain reduction at 6 months after repeated subcutaneous injections of BTX-A that had a better tolerance than other treatments. In addition, they found that the presence of allodynia and a limited thermal deficit might be useful predictors of treatment response, and also proposed a central effect for BTX-A as no difference in the neuropeptide content of skin biopsies at the site of pain was found after BTX-A injections compared to baseline (prior to BTX-A injections).

In addition to the studies supporting BTX-A use for the alleviation of spinal neuropathic pain, there has also been data indicating that BTX-A has specific effects in trigeminal neuropathic pain with only minor and reversible adverse effects. In addition to several case reports,[67,68] favorable effects of BTX-A have been reported by Türk et al[69] in 8 patients and by Borodic and Acquadro[70] in 11 patients. In an open study including 13 patients, BTX-A reduced both VAS pain scores and the size of the painful area.[71] Zúñiga et al[72] treated 12 patients suffering from refractory trigeminal neuralgia who were unresponsive to usual pharmacologic treatment with BTX-A (20—50 U), and the authors reported significant pain relief in 10 patients for an average period of 2 months. Bohluli et al[73] used BTX-A to improve pain in 15 trigeminal neuralgia

patients in terms of frequency and severity of pain attacks, with a complete alleviation in 7 patients. Wu et al[74] assessed the effect of BTX-A (75 U) on trigeminal neuralgia in a RCT in 22 patients vs 20 placebo subjects and observed a significant effect: 68% of the BTX-A patients experienced at least a 50% reduction in pain, compared to 15% in the placebo group. Another RCT involving 20 trigeminal neuralgia patients (10 BTX and 10 placebo) evaluated the effects of BTX-A (40—60 U) vs placebo and found a pain reduction of approximately 75% at 3 months, which was associated with a significant reduction in the frequency of pain paroxysms and significant improvement of quality of life.[75] In a double-blind RCT, Zúñiga et al[76] compared 20 trigeminal neuralgia patients injected with 50 U of BTX-A to 16 trigeminal neuralgia patients treated with placebo. Significant VAS decrease was observed at 2 and 3 months. In a larger study of 88 patients with trigeminal neuralgia, significant pain relief was observed in almost half of the patients after 3 months, and although the therapeutic effect decreased afterwards, effective treatment was still observed at 14 months in 39% of cases, with complete pain management in 22 patients (25% of cases).[77] Zhang et al[78] conducted a RCT in 84 patients that assessed two doses of BTX-A and observed a significant reduction of pain in approximately 75% of the patients at 2 months, vs 32% in the placebo group. More recently, in 87 patients suffering from trigeminal neuralgia, Xia et al investigated the effects of BTX-A injections into the painful area on VAS pain scores and comorbidities.[79] The authors observed a significant improvement of VAS pain scores from 1 to 8 weeks of treatment (in 48% and 80% of patients, at 1 week and 8 weeks, respectively); health-related items were also significantly improved. A recent meta-analysis evaluating the effects of BTX-A on trigeminal neuralgia and postherpetic neuralgia, including four of the aforementioned RCTs, concluded that a significant but moderate effect resulted from the injections.[80]

In the case of PPTTN, the available literature comprises only clinical case reports. In 2010, Yoon et al[81] described one case of PPTTN slightly ameliorated by subcutaneous injection of BTX-A. Cuadrado et al[82] reported four patients presenting persistent trigeminal pain, and intraoral injection of BTX-A resulted in a reduction in pain intensity (from moderate/severe initially to almost complete relief). One of these cases could be classified as PPTTN, while the three other cases would most probably fit the description of idiopathic pain. Although the dental status was not provided, the study suggests that BTX-A could also be effective in this type of pain. Hererro-Babiloni et al[83] described one case of persistent dentoalveolar pain (possibly PPTTN) and one case of trigeminal neuralgia, both of which were effectively relieved following intraoral injections of BTX-A. In sum, the scarce yet interesting available literature clearly underlines the need for further RCTs on BTX-A injections for PPTTN treatment.

Adverse Effects of BTX-A

BTX-A has been widely used with a good safety profile and only a few adverse effects.[84–88] Local adverse effects are mainly pain at the injection site, rash, and edema. Spread of the toxin to nearby tissues is possible and can lead to muscle weakness or paralysis and subsequent facial asymmetry.[72,77,88] Remote effects due to diffusion of the toxin can cause autonomic responses and regional or systemic muscular weakness. Nausea, urinary incontinence, falls, seizures, fever, dry mouth, and dysphagia have also been occasionally reported, mainly in patients with preexisting comorbidities. Adverse effects are generally mild to moderate and transient. Major risks seem related to the total injection dose and injection frequency due to immune reactions against the toxin. Doses greater than 600 U of BTX-A with follow-up injections occurring every 3 months may lead to an increased risk of developing severe adverse events. Furthermore, the use of BTX-A in orofacial pain states might lead to an increased risk of adverse effects as compared to other regions. For example, after orolingual injections of BTX-A, a greater number of adverse events (13% to 19%) were reported than with truncal-axial injections.[89] However, the most frequent adverse events were mouth dryness and dysphagia.

Another adverse effect is the development of immunologic reactions after repeated administrations of BTX-A, which over the years may lead to a loss of clinical response (secondary negative reaction) due to the formation of neutralizing antibodies (NAbs) directed against the neurotoxin. The mean frequency of this effect was evaluated in a systematic and meta-analytic review of patients treated with BTX-A and found to be 12% (varying from 1.1% to 20%, depending on the indication).[90] However, although the prevalence of NAbs was lower (3.5%) among clinically responding patients and higher (53.5%) in patients showing a secondary negative reaction, the development of NAbs did not always predict responsiveness to BTX-A therapy and approximately half of secondary nonresponsive patients did not have NAbs, suggesting that NAbs are not the main cause for loss of clinical response in at least half of the patients. Patients with resistance to one serotype could benefit from injections with another serotype. In order to minimize future immunoresistance, Wheeler and Smith[32] recommended the use of the smallest possible effective dose to extend the interval between treatments as long as reasonable (ie, at least 3 months between injections), and to avoid using booster injections.

Table 1a Studies Reporting the Efficacy of BTX-A for Trigeminal Neuralgia

Study	Study design	n	Diagnoses	Injection route/site(s)/dose
Micheli et al (2002)[92]	Case report	1	TN and HFS	12.5 U, 5 sites, 12-wk intervals
Borodic and Acquadro (2002)[70]	Prospective, open label pilot study	11	TN	25–50 U, 1 to 4 injections at the site of pain
Türk et al (2005)[69]	Randomized, open-case series	8	TN	100 U in 2 sites above and below zygomatic arch
Allam et al (2005)[68]	Case report	1	TN	16 U, 8 sites SC, area of V1 and V2
Volcy et al (2006)[93]	Case report	1	TN and GON	30 U, multiple injections into the GON and TN pain areas at several-month intervals
Piovesan et al (2005)[71]	Prospective, open study	13	TN	3 U per point (total 6–9 U) subdermally in painful area
Boscá-Blasco et al (2006)[94]	Case series	4	TN and HFS	17.5 U at 6-mo intervals
Uluduz et al (2007)[95]	Case report	1	TN	75 U at 3-mo intervals
Felicio et al (2007)[96]	Case report	1	TN and HFS	100 U ipsi and 52 U contra, repeated after 5 mo
Zúñiga et al (2008)[72]	Prospective, open, case series	12	TN	20–50 U SC into TZ (and IM for patients with V3 involvement)
Ngeow and Nair (2010)[67]	Case report	1	TN	100 U, SC, 2 sites; re-injected after 5 mo
Bohluli et al (2011)[73]	Prospective, open, case series	15	TN	50 U into TZ
Wu et al (2012)[74]	Randomized, double-blind, placebo-controlled study	42: 22 BTX/ 20 PLA	TN	75 U intradermally or submucosally into TZ
Shehata et al (2013)[75]	Randomized, single-blinded, placebo-controlled study	20:10 BTX/ 10 PLA	TN	40–60 U, SC into pain area and TZ; larger dose IM when V3 involvement
Zúñiga et al (2013)[76]	Double-blind, randomized, placebo-controlled study	36: 20 BTX/ 16 PLA)	TN	50 U SC ipsi; (+10 U IM when V3 involved)
Zhang et al (2014)[78]	Randomized, double-blind, placebo-controlled study	84: 27 BTX 25 U; 29 BTX 75 U; 28 PLA	TN	25 and 75 U; 20 loci in the pain area; intradermally and/or submucosally
Li et al (2014)[77]	Open-label study	88: (≤ 50 n = 43; 50–100 n = 32; ≥ 100 U n = 13	TN	25–170 U; subcutaneously, submucosally
Xia et al (2016)[79]	Prospective open study	87	TN	15–20 U sites
Batifol and Finiels (2016)[97]	Retrospective study	28	TN	15–50 U Injection covering the painful area (n = 16) or into TZ (n = 12)

AO = atypical odontalgia; BTX = botulinum toxin (type A); GON = great occipital neuralgia; HFS = hemifacial spasm; IM = intramuscular injection; ipsi = ipsilateral to the pain; contra = contralateral to the pain; NP = neuropathic pain; NRS = numeric rating scale (0–10); PLA = placebo; PPTTN = peripheral posttraumatic trigeminal neuropathy; PR = patient report; QoL = quality of life; RCT = randomized controlled trial; SC = subcutaneous injection; TN = trigeminal neuralgia; TZ = trigger zone; VAS = visual analog scale (0–10).

Table 1b Studies Reporting the Efficacy of BTX-A for Other Orofacial Neuropathic Pain States

Study	Study design	n	Diagnoses	Injection route/site(s)/dose
Yoon et al (2010)[81]	Case report	1	PPTTN	10 U SC
Cuadrado et al (2016)[82]	Case series	4	1 PPTTN and 3 AO	PPTTN: 25 U; 10 sites in tooth socket, gums, and hard palate; 15–30 U for AO 6–12 sites in gums and lips
Herrero Babiloni et al (2016)[83]	Case report	1	1 Persistent dento-alveolar pain	100 U, submucosal injections, vestibular sulcus and attached gingiva

AO = atypical odontalgia; BTX = botulinum toxin (type A); GON = great occipital neuralgia; HFS = hemifacial spasm; IM = intramuscular injection; ipsi = ipsilateral to the pain; contra = contralateral to the pain; NP = neuropathic pain; NRS = numeric rating scale (0–10); PLA = placebo; PPTTN = peripheral posttraumatic trigeminal neuropathy; PR = patient report; QoL = quality of life; RCT = randomized controlled trial; SC = subcutaneous injection; TN = trigeminal neuralgia; TZ = trigger zone; VAS = visual analog scale (0–10).

Pain effect	Follow-up	Secondary outcomes	Adverse effects
Pain relief	2 mo		NR
8/11 responders (defined as > 50% reduction in self -reported pain intensity or/and frequency of attacks)	2–6 wk		Temporary facial asymmetry and facial weakness
Reduction in VAS (4 to 1.2) and frequency of attacks (4 to 1.2)	6 mo		None
Reduction in pain in V1, V2, and V3	3 mo		None
> 90% pain relief	10 mo		None
Reduction in pain surface and intensity (VAS) (100% pain free in 4 patients, > 50% in 9 patients)	2 mo		No major side effects
Pain reduction	Every 6 mo		None
Complete pain relief	36 mo		
"Satisfactorily response" (pain relief)	7 mo		None
Reduction in VAS (8.8 to 4) and frequency in 10 patients (83%)	2 mo		Transient facial asymmetry (1 patient)
Complete pain relief at one site, partial in the other	5 mo		No major effect; facial muscle paralysis affecting ability to "blow out" and talk
Reduction in pain intensity (VAS) and frequency in 100% of patients; pain free in 7 patients	6 mo		Temporary partial facial paralysis in 3 patients
Reduction in pain intensity (> 50% VAS) (68% BTX vs 15% PLA) and frequency	3 mo	Global impression of change	22% with short-term facial asymmetry
Reduction in pain intensity (VAS 6.5 BTX vs 0.3 PLA) and frequency	3 mo	Increase in QoL	Transitory facial asymmetry, hematoma, itching and pain at the site of injection
Reduction in pain intensity (VAS 4.7 in BTX vs 6.9 PLA) and frequency of attacks	3 mo		Hematoma in 2 patients; slight facial asymmetry in 2 patients
Pain reduction: 70% (50 U) and 86% (75 U) of BTX vs 32% PLA responders (defined as > 50% VAS reduction); no significant difference between 25 U and 75 U	2 mo		Transient short-term facial asymmetry in 3 patients Transient edema in 2 patients
Pain reduction (VAS and frequency of attacks): effective (> 50% VAS reduction) in 100% at 2 months and 25% at 14 months; no significant difference between groups	17 mo		Transitory swelling at injection sites in 3 patients; facial asymmetry in 10 patients
Pain reduction (VAS) from 6.5 to 3.66 at 1 wk to 1.9 at 8 wk	2 mo	Depression, anxiety, sleep disorders, QoL significantly improved	Local swelling in 2 patients; muscle relaxation in 7 patients
Pain reduction (VAS) 57% no pain after 1 injection 71% need no more injections after 3 mo	24 mo		Facial asymmetry in 3 patients

Pain effect	Follow-up	Secondary outcomes	Adverse effects
Decreased painful area and pain intensity	2 mo		None
PPTTN: Almost complete pain relief AO: Almost or complete pain relief	6–20 mo		None
Pain reduction (NRS): 5 to 2	9 mo		Temporary mucosal dryness and smile droopiness

Mode of Administration and Dosage

Based on the small number of studies and the heterogeneity of protocols, it is difficult to draw strong lines of evidence for the clinical use of BTX-A in PPTTN. For spinal neuropathic pain, BTX-A is mainly administered as multiple injections (intramuscular, subcutaneous, or submucosal) covering the area of the painful site in a mean range of 20 to 200 U, although lower (6 to 9 U) or higher (500 or even 2500 U) doses have been used, depending on the conditions treated.[91] Interestingly, 20-U injections had lower efficacy than 10-U injections for neck neuropathic pain. For trigeminal neuralgia, doses of 6 to 170 U have been used (Table 1) in multiple injections with a significant effect. No significant difference was observed between 25 and 75 U or between ≤ 50, 50 to 100, and ≥ 100 U in two comparative RCTs.[76] Additionally, repetitive administration improved the effect, which might be due to the increase in the quantity of BTX-A available at the injection site.[66] In a retrospective study comparing sites of injections in trigeminal neuralgia patients, no significant difference was found when injecting the painful zone compared to a possible trigger zone.[92]

It may be inferred from these studies that a dose between 25 and 50 U can be advocated for intraoral pain, dividing the total dose in multiple injections in order to cover the main area of pain. Furthermore, it seems reasonable to recommend a slow injection with lidocaine in order to limit pain at the site of injection, a common side effect of BTX-A injections.[61,66] As pointed out by Herrero-Babiloni et al,[83] four important considerations need to be taken into account to reduce the risk of undesirable spread of the toxin:

1. Anatomy (adjacent tissues and structures such as facial planes, blood vessels, glands, swallowing and airway support musculature, and nerves innervating distant structures [ie, phrenic nerve, vagal nerve])
2. Toxin injection volume
3. Use of a vasoconstrictor to limit toxin diffusion
4. Toxin dosage

Conclusions

The relevant reviewed studies and data suggest a potential and promising effect of BTX-A in the treatment of trigeminal neuropathic pain, including PPTTN. Available data emphasize the need for further well-conducted studies in the orofacial region with well-defined inclusion criteria, large sample sizes, and operationalized outcome parameters.

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