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Botulinum Toxin Type A: A Therapeutic Alternative for Trigeminal Neuralgia – A Literature-Based Overview

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ABSTRACT

Trigeminal neuralgia (TN) stands as one of the most prevalent forms of craniofacial pain. It commonly targets the areas supplied by the maxillary or mandibular divisions of the trigeminal nerve. Even the slightest stimulation, such as gentle touch can result in severe pain and incapacitation for the patient.

The etiology of TN encompasses idiopathic, classic, and secondary classifications. The most common form is the classical type.

Carbamazepine and oxcarbazepine are typically the initial pharmacological interventions prescribed for TN, offering relief for many individuals. Considering evidence of varying quality, medications such as lamotrigine, gabapentin, botulinum toxin type A, pregabalin, baclofen, and phenytoin could be viable options, either alone or in combination with carbamazepine or oxcarbazepine, if initial treatments prove ineffective or intolerable.

Botulinum toxin type A therapy has shown high efficacy without severe adverse events in alleviating pain in patients with trigeminal neuralgia.

This article aims to provide a literature-based overview of trigeminal neuralgia, outlining its unique characteristics, etiology, epidemiology, classification, and management especially using botulinum neurotoxin A.

KEY WORDS: botulinum toxins, trigeminal neuralgia, neuralgia, facial pain

INTRODUCTION

The trigeminal nerve, also known as the fifth cranial nerve, is the largest among them and plays a crucial role in feeling stimuli from the face and head region. It divides into three main branches: the ophthalmic nerve (V1), the maxillary nerve (V2), and the mandibular nerve (V3).[1–4]

Trigeminal neuralgia (TN), also traditionally known as tic douloureux [5] is a chronic or episodic craniofacial pain syndrome. It represents one of the most prevalent forms of facial pain, affecting approximately 4 to 13 individuals per 100,000 population.[6–8] This condition manifests with sudden, brief (up to 2 minutes) attacks of intense, electric-shock-like pain that unilaterally affects one or more divisions of the trigeminal nerve (V). The maxillary and mandibular divisions are most commonly involved, with a higher prevalence on the right side of the face compared to the left.[9,10] Even minimal stimulation, such as gentle touch, conversation, or mastication (chewing), can trigger severe pain and significantly impact a patient's daily activities.[6,11] Table 1 outlines the known triggers of TN. Notably, TN affects women at a rate twice that of men and typically presents in individuals over 50 years of age.[12]

Table 1. Frequency of triggers in trigeminal neuralgia.

	Di Stefano, G. et al [13] n (%) in prospective study; n (%) in retrospective study	Maarbjerg, S. et al [14] n (%)
Touching the face	58 (83); 52 (74)	109 (69)
Talking	41 (59); 35 (50)	91 (58)
Chewing	29 (41); 32 (46)	123 (78)
Tooth brushing	25 (36); 19 (27)	104 (66)
Washing one's face	19 (27); 20 (29)	–
Eating	16 (23); 19 (27)	93 (59)
Shaving	7 (10); 13 (19)	–
Drying one's face	8 (11); 10 (14)	–
Swallowing	7 (10); 9 (13)	–
Drinking	6 (9); 7 (10)	–
Jaw movement	6 (9); 5 (7)	–
Blowing one's nose	5 (7); 4 (6)	–
Flexing the trunk forward	4 (6); 3 (4)	–
Hot or cold food/ water	2 (3); 4 (6)	–
Cold wind	–	79 (50)
Laughing	1 (1); 3 (4)	–
Raising own voice	2 (3); 1 (1)	–
Application of make-up	2 (3); 1 (1)	–
Yawning	1 (1); 2 (3)	–
Pronouncing labial letters	2 (3); –	–
Combing	1 (1); 1 (1)	–
Eye movement	1 (1); 1 (1)	–
Washing one's hair	1 (1); 1 (1)	–
Head movements	2 (3); –	–
Tongue movement	–; 2 (3)	–
Sneezing	1 (1); 1 (1)	–
Cough	1 (1); –	–

Loud noises	–	<3 (<0,02)
Emotional stress	–	<3 (<0,02)
Physical exercise	–	<3 (<0,02)
Movement of the ipsilateral upper limb	–	<3 (<0,02)

CLASSIFICATION OF TRIGEMINAL NEURALGIA

Trigeminal neuralgia can be categorized into three main types based on the underlying etiology: idiopathic, classical (trigeminal sensory neuropathy), and secondary.

Classical Trigeminal Neuralgia is the most common form of TN, affecting the majority of patients. It arises from compression of the trigeminal nerve root at the brainstem by intracranial blood vessels, typically the superior cerebellar artery. This compression is thought to cause demyelination, a process where the protective fatty sheath surrounding nerve fibers is damaged. Additionally, it can lead to dysregulation of voltage-gated sodium channels (VGSCs) within the nerve membrane. These combined changes contribute to the characteristic excruciating pain experienced by patients with TN.[5,15]

Secondary Trigeminal Neuralgia makes up about 15% of TN cases and is caused by an identifiable underlying neurological condition. Examples include multiple sclerosis or tumors located in the cerebellopontine angle, the region where the brainstem meets the pons. These conditions can either affect the area where the trigeminal nerve enters the brainstem compress the nerve along its pathway outside the skull.[5,16] While both classical and secondary TN share similar clinical features, patients with secondary TN often present at a younger age. They may also experience sensory loss in specific areas of the face and are more likely to have pain on both sides of the face.[17]

Idiopathic Trigeminal Neuralgia represents approximately 10% of TN cases and has no identifiable cause for the nerve dysfunction. The exact reason for the pain in these cases remains unknown.[5]

TREATMENT OF TRIGEMINAL NEURALGIA

Carbamazepine (CBZ) and oxcarbazepine (OXC) are the mainstay of initial pharmacological therapy for trigeminal neuralgia, providing pain relief for many patients. [15] In long-term management, carbamazepine (dosage range: 200-1200 mg/day) or oxcarbazepine (dosage range: 300-1800 mg/day) are often the preferred first-line medications, particularly during treatment initiation. Higher doses may be necessary in some cases. However, if these

medications are ineffective or cause unacceptable side effects, alternative drug options should be considered.

Due to the variable quality of evidence, medications such as lamotrigine, gabapentin, botulinum toxin type A, pregabalin, baclofen, and phenytoin may be considered as alternative or adjunctive therapy if initial treatment fails or is poorly tolerated due to efficacy or side effects.[17,18]

While carbamazepine is widely considered the first-line medication for TN, its use can be limited by a higher rate of discontinuation due to side effects such as drowsiness, dizziness, rash, potential for liver damage, and ataxia. Additionally, the potential for carbamazepine to interact with other medications can further complicate its use.[19–21]

SURGICAL TREATMENT

Surgical intervention becomes a consideration for patients with trigeminal neuralgia who experience severe symptoms, demonstrate inadequate response to medications, or suffer from recurrent pain episodes or intolerable side effects from medication. These procedures aim to alleviate pain by addressing the underlying cause or disrupting the pain pathway. These procedures encompass microvascular decompression, gamma knife radiosurgery, and various percutaneous techniques such as glycerol rhizotomy, radiofrequency thermocoagulation, and percutaneous balloon compression.[22–27]

BOTULINUM TOXIN TYPE A

Although clinical experience is limited, some evidence suggests that Botulinum toxin type A (BTX-A) may serve as an adjunct therapy for trigeminal neuralgia in certain cases. A low-level recommendation, based on very low-quality evidence, supports the use of BTX-A as an add-on treatment for the medium-term management of TN.[17,28,29]

BTX-A is a potent neurotoxin derived from certain strains of Clostridium botulinum bacteria. [30] BTX-A acts by inhibiting the release of acetylcholine at the neuromuscular junction, leading to muscle relaxation. [31] However, in the context of TN, studies suggest a broader effect. BTX-A may also influence the release of pain-related neuropeptides such as substance P and calcitonin gene-related peptide by affecting neuronal synaptic vesicles. [32,33] Additionally, it might decrease the expression of transient receptor potential vanilloid type 1 (TRPV1) receptors on peripheral nociceptors, potentially reducing inflammatory pain sensitivity.[33,34] BTX-A should be injected in the pain area.[35]

COMPARISON OF BOTULINUM TOXIN TYPE A EFFICACY IN TRIGEMINAL NEURALGIA TYPES 1 AND 2

One study investigated the efficacy of BTX-A in TN. Forty patients participated, with 18 diagnosed with Trigeminal Neuralgia Type 1 (TN1) and 22 with Trigeminal Neuralgia Type 2 (TN2). After a one-month follow-up, seven patients (17.5%) achieved complete pain relief (four with TN1 and three with TN2). At the three-month follow-up, six patients remained pain-free (four with TN1 and three with TN2). The treatment demonstrated significant pain reduction in 62.5% of patients (25 patients). These findings support the notion that BTX-A is an effective and safe treatment for TN patients. Importantly, patients with TN1 and TN2 exhibited no statistically significant differences in their treatment response to BTX-A in terms of pain intensity.[36]

MEDIUM DOSAGE OF BTX-A

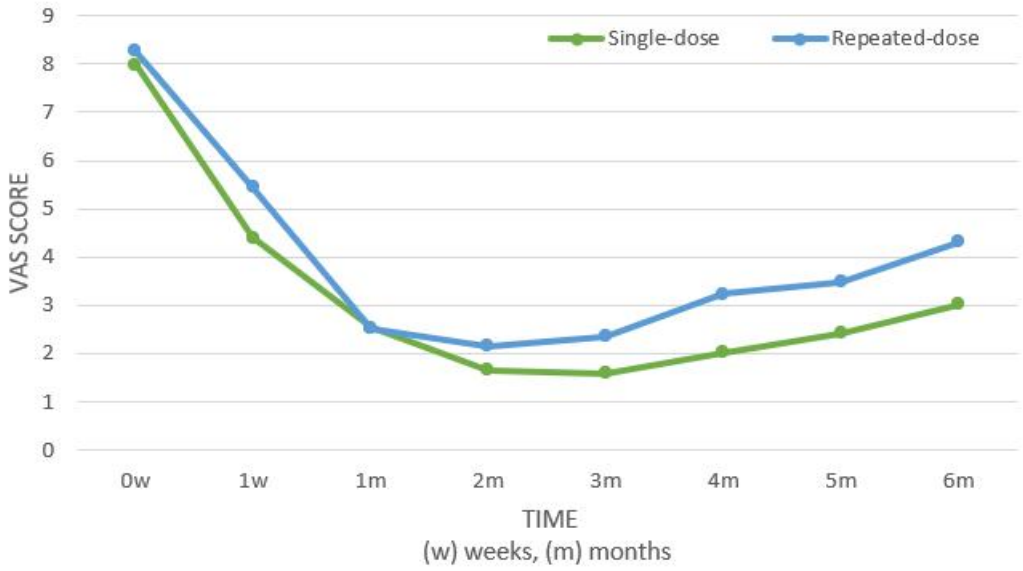
In clinical practice, the typical medium dosage of BTX-A ranges from 25 to 100 units, as documented in various studies. [17] However, some studies have reported a wider range, spanning from 50 to 100 units. [37,38] One randomized, double-blind, placebo-controlled trial investigated the efficacy of local multi-point injections of BTX-A in 84 patients with classical trigeminal neuralgia using varying doses. Patients were randomly assigned to receive either a placebo or BTX-A at doses of 25 units or 75 units. Follow-up assessments were conducted weekly for eight weeks following injection to evaluate pain severity, efficacy, and adverse reactions. The results indicated that both the lower dose (25 units) and higher dose (75 units) demonstrated similar short-term efficacy. However, the long-term equivalence between the two doses remains unclear.[39]

SINGLE-DOSE VERSUS REPEATED-DOSE

No standardized dosing regimen has been established for the treatment with BTX-A. In one study patients were randomly allocated to receive either a single dose or multiple doses of BTX-A. In the single-dose group, patients received a local injection of 70-100 units of BTX-

A at the site of pain. The repeated-dose group received an initial injection of BTX-A followed by another injection two weeks later. Each dose ranged from 50-70 units, with a total dosage of 100-140 units. All patients were monitored for six months and had the right to withdraw from the study at any time. The study found that the efficacy and safety of both single and repeated BTX-A dosing regimens were largely similar. This suggests that repeated dosing does not provide any significant benefit over single dosing for trigeminal neuralgia. Ultimately, the appropriate dosage should be individualized for each patient.[38]

Figure 1. VAS score after 6-month treatment with single dose BTX-A and repeated-dose BTX-A



SIDE EFFECTS ASSOCIATED WITH BTX-A TREATMENT

Treatments with BTX-A are typically associated with a low incidence of adverse events. The reported side effects were mostly mild and resolved spontaneously without further intervention. No adverse events affecting the whole body (systemic reactions) or serious injection-related complications were observed in the studies. Table 2 summarizes the adverse reactions reported in previous investigations.

Table 2. Adverse reactions associated with BTX-A treatment

Study	Total number of patients	Side effects (number of patients)
Türk Ü et al. [40]	8 treated with BTX-A	Dysesthesia on the side of the injection (1 treated with BTX-A). Difficulty in chewing on the side of the injection (1 treated with BTX-A).
Zúñiga, C et al. [41]	20 treated with BTX-A; 16 received placebo	Hematoma at the site of administration (2 treated with BTX-A). Slight facial asymmetry due to weakness (2 treated with BTX-A).
Zhang, H et al. [38]	44 treated with single dose of BTX-A; 37 treated with repeated dose of BTX-A	The type of adverse reactions has not been described in the study (7 treated with single dose of BTX-A, 7 treated with repeated-dose of BTX-A).
Gazerani, P et al. [42]	14 treated with BTX-A	No side effects reported.
Zhang, H et al. [39]	25 treated with 25U of BTX-A; 28 treated with 75U of BTX-A; 27 received placebo	Short term facial asymmetry in the injection area during dynamic movement (2 in 25U BTX-A group, 1 in 75U BTX group). Transient edema in the injection area (2 in 25U BTX-A group).
Shehata, H et al. [43]	10 treated with BTX-A; 10 received placebo	Facial asymmetry (4 treated with BTX-A) Hematoma at the site of injection (1 treated with BTX-A, 2 received placebo). Itching at the site of injection (1 treated with BTX-A, 1 received placebo). Pain at the site of injection (1 treated with BTX-A, 1 received placebo).

Wu, C et al. [44]	22 treated with BTX-A; 20 received placebo	Facial asymmetry on the injection area (5 treated with BTX-A). Transient oedema on the area of Injection (3 treated with BTX-A, 1 received placebo).
Xia, J et al. [35]	87 treated with BTX-A	Local swelling in the injection sites (2 treated with BTX-A). Muscle relaxation in the injection sites (7 treated with BTX-A).
Bohluli, B et al. [37]	15 treated with BTX-A	Transient paresis of the buccal branch of the facial nerve (3 treated with BTX-A).
Piovesan, E. et al. [45]	13 treated with BTX-A	No major side effects.
Tereshko, Y et al. [36]	40 treated with BTX-A	Facial asymmetry (14 treated with BTX-A).

CONCLUSION

Botulinum toxin type A therapy has shown high efficacy in alleviating pain in patients with trigeminal neuralgia. It also leads to improvements in anxiety, depression, and sleep quality, contributing to an overall improvement in quality of life. This treatment approach represents a safe and effective option for managing trigeminal neuralgia. However, further studies are warranted to strengthen the existing evidence supporting the use of BTX-A in treating this condition.

Disclosure

Author's contribution

Conceptualization: Natalia Wierzejska and Mikołaj Domański; Methodology: Barbara Kopczyńska and Maria Wojcieszek; Software: Oliwia Czyżniewska; Check: Karina Otręba; Formal analysis: Barbara Kopczyńska; Investigation: Natalia Wierzejska and Mikołaj Domański; Resources: Karolina Czupryńska and Julia Szałajska; Data curation: Barbara Kopczyńska and Maria Wojcieszek; Writing - rough preparation: Natalia Wierzejska and Mikołaj Domański; Writing - review and editing, Karolina Czupryńska; Visualization: Oliwia

Czyżniewska and Julia Szałajska; Supervision: Mikołaj Domański; Project administration: Karina Otręba; Receiving funding - no specific funding.

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The authors deny any conflict of interest.

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