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Botulinum Toxin A Therapy for Temporomandibular Disorders

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DEFINING TEMPOROMANDIBULAR DISORDER

Temporomandibular disorder (TMD) is a collective term used to describe a group of pathologic conditions involving the temporomandibular joint (TMJ), masticatory muscles, and/or associated structures. As such, the TMDs encompass a wide variety of medical disorders of orthopedic and myofascial origin that closely resemble those described for other joint and muscular conditions. The unique nature of TMD resides in the proximate anatomy of numerous other facial and cranial structures, thereby complicating, interacting with, and mimicking other sources of head and neck pain (Figs. 25.1 and 25.2).

Symptoms commonly associated with TMDs include:

- Difficulty speaking
- Difficulty eating
- Difficulty sleeping
- Chronic headaches
- Earaches, hearing impairment
- Jaw dysfunction including hyper- and hypomobility
- General orofacial pain

The differential diagnosis for TMD is a gallery of conditions applicable to almost all head and neck pain. Table 25.1 provides an incomplete list (1).

An historical review by Kaplan (2) reveals that TMD was described as early as 1920 in the guise of ''abnormalities of mandibular articulation'' (Wright, 1920; Goodfriend, 1933). Subsequent nomenclatures for TMD and its subtypes reinforce the observations, vanities and biases of the investigators, including:

- Costen's syndrome (Costen, 1956)
- TMJ dysfunction syndrome (Schore, 1959)
- TM pain syndrome (Schwartz, 1959)
- Pain dysfunction syndrome (Voss, 1964)
- Myofacial pain dysfunction syndrome or MPDS (Laskin, 1969)
- Myoarthropathy of the TMJ (Graber, 1971)
- Occlusomandibular disturbance (Gerber, 1971)
- Internal joint derangement (Farrar, 1971)

Statistics from epidemiologic studies are difficult to compare as a universally accepted classification system for TMD does not exist (see below). De Kanter and coworkers published the results of their meta-analysis of 51 studies in 1993 (3). The results were confounded by some limitations, including a lack of uniformity in classification. However, more than 15,000 subjects in 23 studies reported a dysfunction rate of 30%. Professionally assessed dysfunction was identified in 44% of subjects. While the statistics may be difficult to pin down, it is clear that TMDs are common in nonpatient populations (4).

Thorough reviews of data from large studies reveal that 20% to 25% of a population (5,6) sought professional care for their TMD at some point in their life. Significantly, advanced care requiring the expertise of specialists was required in 5% to 10% of the population (7–10). The economic and societal costs are substantial (11).

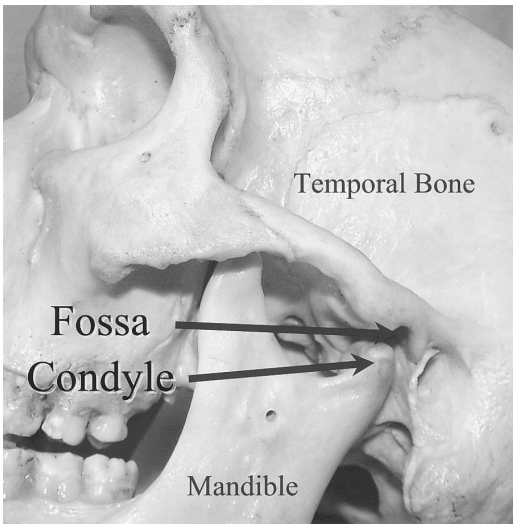

FIG. 25.1. The Joint

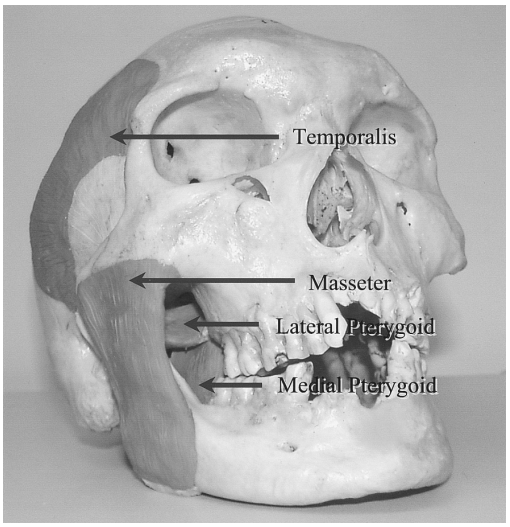

FIG. 25.2. The Musculature

CLASSIFICATION OF TMD

At this writing, there exists no unanimity in the TMD community regarding a single universally acceptable taxonomy. A comprehensive, historical overview and analysis by Ohrbach and Stohler (12) of proposed systems include Bell, 1960, 1982, 1986; American Academy of Craniomandibular Disorders, 1980, 1990; Block, 1980; President's Conference on the Examination, Diagnosis and Management of TMJ Disorders, 1982; Farrar, 1982; Eversole and Machado, 1985; Fricton, 1988; International Headache Society (fits ICD system), 1988; Stegenga et al. (based on system of American Rheumatism Association), 1989; and Research Diagnostic Criteria (RDC), 1992. Currently, the RDC and ICD systems appear to be used more commonly than any of the others.

Despite the differences, a practical review of these classification systems yields several common underlying themes. First, while most of the schemes attempt to provide comprehensive coverage of all possible pathologic conditions, the most prevalent clinical TMDs are primary craniomandibular pains. These are usually divided, based upon anatomic etiology, among pain originating in the TMJ proper or intracapsular (i.e., arthrogenic) and pain originating in the muscula-

TABLE 25.1. *Differential diagnosis of TMD*

Source of pathology	Common examples
Systemic diseases	Multiple myeloma; diabetes mellitus; systemic lupus erythematosus (SLE); giant-cell arteritis
Myofascial pain	Masticatory muscles; cervical muscles; frontalis-occipitalis and other facial muscles involved in tension headaches, cervicogenic headaches, myofascial pain dysfunction (MPD), fibromyalgia
Skeletal pain	Osteomyelitis; neoplasia; fibrous dysplasia; gout; osteomalacia; Paget's disease
Proximate anatomic structure pain	Odontogenic; ophthalmic; otic; nasal; sinus; salivary; Eagle's syndrome
Intracranial pathology	Neoplasm; aneurysm; abscess; hemorrhage; hematoma; edema
Neurologic disorders	Migraine variants; cluster headaches; neuralgias; paroxysmal hemicrania; cranial arteritis; carotidynia
Psychogenic pain disorders	Psychotic syndromes; mood disturbances; anxiety disorders; organic disorders; somatoform disorders

ture (i.e., myogenic). Second, there is a notable overlap between TMD taxonomy and those of other disciplines caring for patients with primary head and neck pain (below). Third, stress, psychologic factors, and chronicity are common and significant factors in TMD, as with most complicated head and neck pain. The contribution of central input and neuroplasticity is significant and must be considered in the successful diagnosis and management of TMD.

INTERDISCIPLINARY MANIFESTATIONS OF TMD

A studied approach transcending medical and dental disciplines yields numerous instances of overlap that have historically resulted in the artificial segmentation of TMDs. Three poignant examples are presented.

Tension headaches (TH): The majority of TH anatomically originate or involve the temporalis and/or masseter muscles. As such, there is no distinction between the classification of this clinical phenomenon as a myogenous TMD versus a TH. It is of little coincidence that some TH researchers use temporalis muscle pain induced by tooth clenching as a valuable experimental model (13).

Oromandibular dystonia: Belonging to the group of movement disorders characterized by involuntary spasms and muscle contractions that induce abnormal movements and postures, this particular subset constitutes a focal form that involves the musculature of the masticatory apparatus and lower face. It manifests as distorted oral position and function resulting in difficulty in speaking, eating, swallowing, and facial appearance. Although it is a neurologic disorder, there is no doubt of its inclusion as a subset of TMDs owing to the involvement of the masticatory apparatus.

Bruxism: This clinical entity may occur as a solitary form of TMD involving only the musculature or as an initiating and/or perpetuating factor in more involved forms of TMD involving joint damage. Taking a wider view of the literature brings an interesting correlation. Bruxism manifests many of the characteristics of dystonia including similar epidemiology, as well as the features of pain and exacerbation by external factors such as fatigue, stress, and emotional extremes. Wooten-Watts, Tan, and Jankovic (14) postulated the possibility that bruxism may be a form of dystonia. With this knowledge, it is entirely possible to view the current treatment of bruxism with intraoral appliances or occlusal adjustments as ''sensory tricks'' that relieve the dystonia. Perhaps this explains the success of a myriad of splint designs and occlusal therapies despite the lack of fundamental understanding of their basis of action. It may also explain the common failure of splint and occlusal therapies in some TMD cases. After all, the sensory trick is not the same for all patients with dystonias.

PATHOPHYSIOLOGY OF TMD

The masticatory system is a dynamic one involving joint, musculature and supporting structures. A simple etiology for TMD is not usually found. Rather, it is a combination of factors that lead to overuse or abuse of the apparatus and resultant pain (15–18). These factors include:

- Parafunctional muscle activity (e.g., bruxing, clenching)
- Trauma (e.g. whiplash, subluxation)
- Psychological factors
- Occlusion
- Systemic diseases (e.g., arthritis)

In the majority of cases, TMD may be considered to be a multifactorial disease.

TREATMENT OF TMD

The range of treatment modalities available for the treatment of TMD is as extensive as the presentations of the different disorders found under this umbrella. It is not surprising, therefore, that there is no consistently effective method of treatment. However, directed treatment of the arthrogenic and myogenic components often yields success, as these are the most common cause for patient presentation (19).

Treatment of joint pathology includes supportive care, indirect joint care and direct intervention. Supportive care includes pharmacotherapy, rest, physical therapies, and psychotherapy

(20–23). Indirect joint care techniques take advantage of the fact that the dentition is an appendage of the mandible as are the TMJs. Manipulation of the teeth and mandible can affect the TMJ. Therefore, orthotics such as oral splints and alterations of the dentition and its alignment can be used to change joint function (24,25). Finally, surgical intervention in the form of arthrocentesis, arthroscopy, and open arthrotomy are available for the advanced correction of arthrogenic pathology (26–29).

The care of the myogenic component of TMD has been limited largely to supportive care. Physical therapies, oral pharmacotherapy, biofeedback, and other modalities usually provide short-term and inadequate relief in more severe cases. However, the importance of muscle therapy is significant because the majority of TMD cases include a myogenous component as an etiologic and/or perpetuating factor. Relaxation of the appropriate muscles yields significant therapeutic gains due to direct muscle effects and indirect joint effects (30–32). Therefore, an ideal agent would provide enduring and specific muscular therapy with an acceptable side effect profile. Botulinum toxin type A (BTX-A) would appear to fulfill these criteria better than any other currently available modality.

Because most patients present with simultaneous arthrogenic and myogenic aspects to their TMD, best results are obtained when providing care for both the concurrently.

EVOLUTION OF BTX-A THERAPY FOR TMD

The long history of BTX-A treatment of movement disorders led to the early treatment of the oromandibular dystonia subset of TMD by pioneers in the field [Blitzer et al. (33), Brin and Blitzer (34), and Tan and Jankovic (35)]. Success in the form of improved function and amelioration of cosmetic disability was demonstrated. Even more significantly, early evidence of pain relief was reported. In light of the similarities between bruxism and dystonias, an attempt to treat bruxism with BTX-A followed. The innovators have reported early successes with this therapy for bruxism (36,37).

Concurrent basic scientific evidence of BTX-A effects beyond the neuromuscular junction supports the unfolding picture of a therapy that has broad-reaching significance for the treatment of pain.

Muscle spindle: Sensory motor transmission is affected by BTX-A (38). Afferent muscle spindle discharge is modified and intrafusal muscle spindles atrophy in response to BTX-A (39). These studies support an afferent mechanism of BTX-A that may play a role in pain modulation.

Antinociceptive effects: Cui and Aoki (40) observed that subcutaneous BTX-A prophylaxis effectively relieved pain associated with formalin-induced inflammation in rats. This report further supports the hypothesis that BTX-A possesses an antinociceptive effect that is independent of its effects on neuromuscular transmission.

CNS effects: Aoki (41) demonstrated a retrograde neuronal uptake of radioactively labeled BTX-A into the central nervous system (CNS). Ishikawa and colleagues (42) observed that BTX-A inhibits the release of substance P from trigeminal nerves. BTX-A may also act via a central mechanism after retrograde transport into the CNS.

The association of pain relief with BTX-A therapy for movement disorders and bruxism provided an early glimpse into the potential for this therapy for complicated TMDs. Fundamental principles of myofascial pain overlay on the joint pathology, chronic myofascial pain, reduction of joint loading by diminution of the activity of the major jaw-closing muscles, and enhancement of postsurgical physical rehabilitation were daily, unresolved clinical challenges that resulted in failures of treatment. The promise of a comprehensive, long-lasting therapy was worthy of investigation.

To date, the only published TMD clinical work has been produced at The Crown Institute and its predecessor. Three studies were undertaken in the past few years.

Feasibility Study

Using the past experience from the dystonia field and dosages used in the masticatory muscles in

oromandibular dystonias, a handful of patients were recruited for a proof-of-concept trial (unpublished). Despite the fact that these patients had the most severe forms of TMD that were resistant to other treatments, the early findings were encouraging. All of the patients experienced a clinical effect ranging from weakened chewing muscles to profound and prolonged pain relief.

Two unexpected findings were identified. The multiple injections into already aching muscles were very painful for some patients, to the extent that they refused follow-up BOTOX injections without some form of sedation/anesthesia. Second, injection of BOTOX only into the clinically symptomatic muscle(s) resulted in a compensatory overactivity and pain in the agonist muscles. This mirroring effect, also seen in cervicogenic headaches, compelled bilateral injection of the musculature subsequently. Finally, particular note was made of the importance of chronicity and complexity of the pain. The more chronic pain sufferers obtained less relief qualitatively. Furthermore, few of the subjects experienced pure myogenic pain. Most had concomitant arthrogenic pain and experienced chronic headaches, including tension and migraine headaches. This observation would consistently repeat in future work in this field and is consistent with findings in the headache field where chronic sufferers rarely present with pure headache forms.

Preliminary Study

This first clinical trial (43) was undertaken to objectively demonstrate the effectiveness of BOTOX in providing relief of symptomatology associated with TMD and to begin to establish a dose response curve (Table 25.2).

TABLE 25.2. *Outcomes for 150 patients randomized to 100 U or 150 U BOTOX*

	Low dose group ($n = 8$)	High dose group ($n = 11$)
Improvement	25%	91%
No change	75%	9%
Worse	0%	0%
Mean onset (weeks)	2.0	1.2
Mean duration (weeks)	3.0	6.2

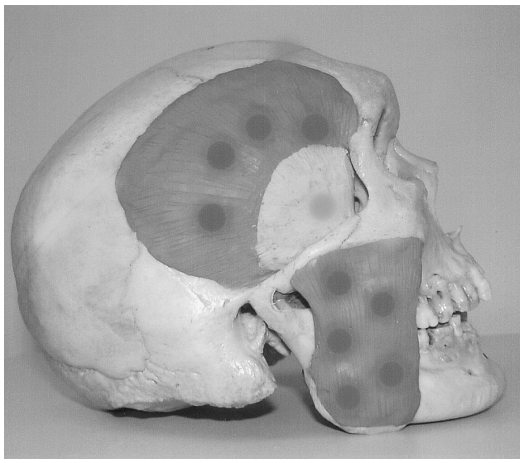

FIG. 25.3. Injection Sites: Masseter and Temporalis

Nineteen patients (mean age, 31 years) were recruited for this randomized study that was neither controlled nor blinded. Eight patients received a total of 100 U of BOTOX distributed equally to the two masseter and two temporalis muscles (Fig. 25.3). Each muscle received five injections of 5 U BOTOX (diluted to 5 U/0.1 cc) delivered via percutaneous injection under EMG guidance. The remaining 11 patients received the same dose to the temporalis muscles and double the dose (50 U) to each masseter muscle in the form of five injections of 10 U BOTOX (diluted to 10 U/0.1 cc) for a total of 150 U BOTOX per patient. All patients were followed for 3 months using numerous objective and subjective criteria.

This preliminary study demonstrated several significant findings:

- No toxicity or side effects were encountered by any patient despite the use of doses up to 3 times the amounts previously reported for the treatment of dystonias involving these muscles.
- There was a dose-dependent, statistically significant difference in clinical improvement indices between the two groups. Despite the small sample size, statistical significance was most likely attainable as a result of the profound difference between the group responses.

The dosage for the two groups differed by a full 50%.
- The speed of onset and duration of action trended toward dose dependence.

The details of this study were published in 1998 (43). The encouraging results prompted three important sequelae. First, BTX-A treatment became an important, albeit experimental, adjunct in the treatment of TMD for patients with chronic pain with a myogenic source. Its utility for nonsurgical patients, as well as pre- and postsurgical patients, proved clinically significant. Second, addressing patient needs became more achievable, but accurate diagnosis became more important. BTX-A seemed to have only an indirect effect on arthrogenic pathology, perhaps by unloading the joint as a result of a reduction in jaw-closing muscle strength, but a more direct effect on myogenic pain and chronic pain. Treatment exclusively with BTX-A for a combined (arthrogenic and myogenic) TMD could not yield relief as good as BTX-A combined with directed joint care. Third, a need for a follow-up study with refinements and a larger sample size was indicated.

Coincidentally and importantly, many of these patients who reported a prior medical history of headaches described profound improvement or prevention during the course of the study.

Pilot Study

This follow-up clinical trial (44,45) was designed to correlate treatment effect to different TMD diagnostic subcategories, to assess clinical correlates such as psychological and demographic profiles, and to establish a temporal relationship between follow-up measures (objective pain, subjective pain, maximum contraction, range of motion) and muscle relaxation.

Fifty subjects with TMD were recruited and 46 completed the study. The design was prospective with no controls as the very effective dose of 150 U of BOTOX (high-dose group above) established previously was used for all patients. The mean age was 40.5 years (range, 16 to 75 years). Each patient was followed at 2-week intervals for a total of 8 weeks. Outcome measures included pain by visual analog scale (VAS), tenderness to palpation, functional index based on multiple VAS, interincisal oral opening, and mean maximum voluntary contraction (MVC) as measured with a custom strain gauge device.

Preliminary results were published in 1999 in the *Journal of Oral and Maxillofacial Surgery* (44), and final results were reported in 2000 in the *British Journal of Oral and Maxillofacial Surgery* (45). In summary, the following significant findings are enumerated:

- Statistically significant improvement from pretreatment levels in pain experience, tenderness to palpation, functional index, and mouth opening were observed.
- These outcome measures remained significantly different from the pretreatment findings at 8 weeks.
- No significant difference was found between diagnostic categories, and between demographic and psychological profiles.
- MVC initially diminished but then returned to pretreatment values.

This study strongly demonstrates that BTX-A therapy produces a reduction in symptoms and an improvement in functional abilities for patients with TMD. The prospects for this new modality of TMD care were clearly positive. An advanced study was indicated and a Phase II multicenter clinical trial began in 2001 with support from Allergan Inc. of Irvine, California (makers of BOTOX).

An apparently paradoxical finding of this study was that all measured patient improvements extended temporally beyond the muscle-relaxing effects as measured objectively by the bite meter. This fact belies the simplistic notion of BTX-A having purely a muscle-relaxing effect, and, along with other recent, disparate observations regarding BTX-A use in treating migraines and its effect on locations other than the neuromuscular junction (e.g., nociceptive afferents), leads one to search for broader understanding of the observed phenomena. A unifying hypothesis is presented below.

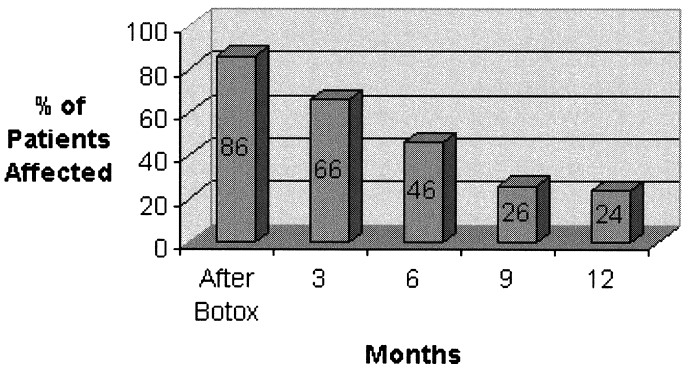

FIG. 25.4. Patients affected by BOTOX vs. time.

Long-term Follow-up

Seventeen patients have now been followed for more than 1 year. While this is not a part of any official study, the observations are presented in chart form (Fig. 25.4). Improvement within 2 weeks following BOTOX injections in almost 90% of patients is a consistent finding in practice. The effect lasts from 1 to 3 months, usually dependent on severity of the TMD. The plateau at approximately 25% beyond 9 months is interesting and may be significant. This is either demonstrative of the natural extinction of the disease or a truly profound long-term effect of BTX-A therapy. Further studies are warranted.

FINAL THOUGHTS: MAKING SENSE OF IT ALL

On cursory examination, it is easy to view BTX-A therapy as a simple muscular agent that has found utility in another orthopedic application, i.e., relating to the TMJ. TMD, however, is not a simple orthopedic problem. It is often associated with headaches and cervicogenic pain. BTX-A's effectiveness extends beyond the muscle-relaxing effect. BTX-A is also useful in treating other head and neck primary pains such as migraine. There is a commonality between TMD, headaches, and neck pain in presentation and response to treatment. These cannot all be coincidental. Furthermore, there is pain relief and functionality that outlasts the muscle relaxant effect of BTX-A. A unifying model based upon known neuroanatomy, neurophysiology, and current understanding of TMD, headaches, and cervicogenic pain is presented.

The trigeminal nucleus (TN), with emphasis on subnucleus caudalis and interpolaris, receives almost all primary afferent input from all of the craniofacial structures, including the intracranial vasculature and dura. It also receives input from the cervical region and cranial nerves VII, IX, X, and XII. Unique to the TN, as compared to spinal nerves, is this extensive convergence pattern of cranial and cervical nerves. Further input to the nucleus is provided from higher centers, many times in the form of inhibitory and regulatory influences.

Second-order afferent neurons synapse within the nucleus and project extensively to other parts of the brainstem and higher centers. Some of these neurons are involved in multisynaptic brainstem paths that function in craniofacial and cervical muscle reflex pathways, as well as autonomic reflex responses. The filtered afferent nociceptive signals ultimately project to the cortex for interpretation as pain. An excellent review with extensive and thorough referencing is provided by Sessle (46). In summary, the TN is the first gateway for afferent head and neck input with wide-ranging integrative function and significant output activity directly through the brainstem and indirectly through higher centers.

The modulation of nociceptive transmission in the TN bears significance in clinical practice as numerous pain phenomena can be explained at the cellular level. Peripheral sensitization, ex-

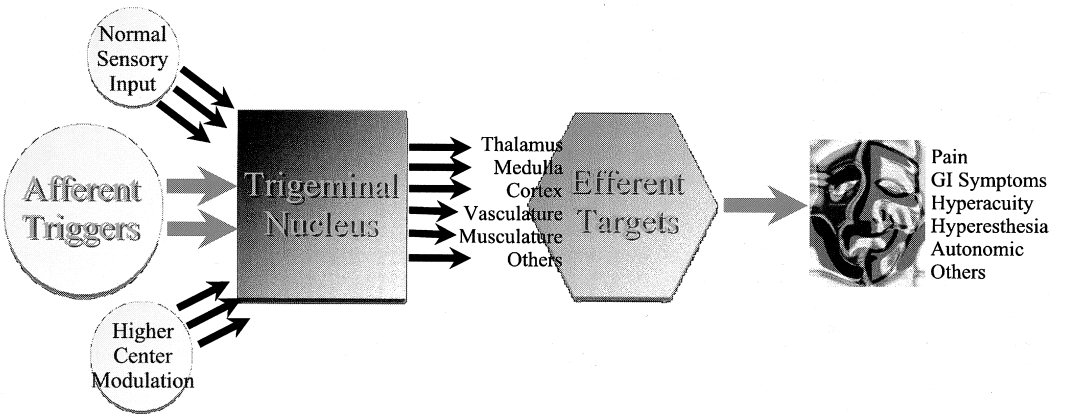

FIG. 25.5. A model of trigeminal nucleus functional trigeminopathy

pansion of receptor fields, recruitment of A-beta fibers and wind-up are all understood in the context of the function of the TN and its constituent parts.

TRIGEMINOPATHY: DEFINITION

The term ''trigeminopathy'' is intended to unify current understanding of primary head and neck pain. It builds on the knowledge base that exists and is therefore consistent with current thoughts on the diagnosis, classification and treatment of these pains. It is defined as a diverse group of primary head and neck pains that share these features:

- Afferent trigger(s) stimulation
- TN stimulation
- Receptive efferent target(s) activation

The afferent triggers may be peripheral or central and are usually a combination of both. In a state of homeostasis, the TN continuously receives numerous inputs, both excitatory and inhibitory in nature, that result in an output which signals normalcy. There is a sense of balance. In a headache sufferer, this balance is upset beginning with an afferent barrage. This afferent overdrive is triggered only in susceptible individuals. In migraine sufferers the result of a stimulus (often peripheral such as food) is an intracranial vascular response mediated, in susceptible individuals, by a channelopathy that results in an excitatory neural message barrage to the TN. This results in a stimulation of the TN. The TN performs an integrative function that results in selective efferent output, both central and peripheral. In people who have receptive efferent targets, their activation manifests as a clinical sign or symptom. The susceptibility of efferent targets is variable within and between individuals. In the case of migraine, centers in the hypothalamus, the periaqueductal gray, raphe nuclei, red nucleus, and others have been identified with positron emission tomography (PET) scans and magnetic resonance imaging (MRI) to be responsible for symptoms such as aura, nausea and vomiting, photophobia, phonophobia, and more [reviewed recently by Hargreaves and Shepheard (47)]. This same schema may be used to understand TMD and cervicogenic pain.

The philosophic significance of trigeminopathy lies in the fundamental shift from the current practice of diagnosis of head and neck pains based on symptomatology, especially difficult because of efferent variability, to a mechanistic diagnosis based on the underlying physiologic disturbance. The core commonality is the TN and its integrative function. Almost all afferent input is funneled into the TN, and almost all efferent outcomes commence at the TN.

Just as the medical community now understands the term ''coagulopathies'' to be a group

of related abnormalities pertaining to our hemostatic system, so trigeminopathies refers to a group of related abnormalities pertaining to pain mechanisms of the head and neck. Perhaps this new understanding will be one of the more significant legacies of BTX-A treatment of primary head and neck pain.

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