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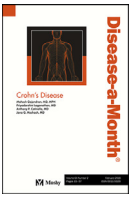

# Trigeminal neuralgia and persistent idiopathic facial pain (atypical facial pain)

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## Introduction

Trigeminal neuralgia (TN), often has an initial presentation within a primary care environment. This evolves into a challenge and becomes difficult to both diagnose and treat. It is frequently misdiagnosed as there are at least three subtypes. Treatment may be multifactorial. The following information is provided to address these challenges.

The diagnostic criteria for Trigeminal neuralgia per the International Classification of Headache Disorders, Edition 3 (ICHD-3):[1]

(A) Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C.
(B) Pain has all of the following characteristics:
  (1) Lasting from a fraction of a second to 2 min.
  (2) Severe intensity.
  (3) Electric shock-like shooting, stabbing, or sharp in quality.
(C) Precipitated by innocuous stimuli within the affected trigeminal distribution.
(D) Not better accounted for by another ICHD-3 diagnosis.

## The Anatomy and physiology of the trigeminal nerves[2]

The three branches of the trigeminal nerve (V1-ophthalmic, V2-maxillary, and V3-mandibular) are involved, with trigger zones found on the skin as well as intraorally. While

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mainly sensory, the trigeminal nerve is the motor nerve for the muscles of mastication, other small muscles, and it is the main sensory nerve of the face and head. The motor nucleus of the trigeminal nerve lies in the pons, and the other muscles innervated include the mylohyoid, the anterior belly of the digastric muscle, the tensor palati, and tensor tympani.

The trigeminal nerve carries general somatic afferent fibers that include exteroceptive sensations, including pain, touch, and temperature) from the skin of the head and face, mucous membrane of the mouth, nasal cavity, meninges, etc., and terminate in the trigeminal nerve's primary sensory nucleus and spinal nucleus.

Proprioceptive sensations from the muscles of mastication, temporomandibular joint, and teeth are also carried. They terminate in the mesencephalic nucleus of the trigeminal nerve and the reticular formation of the brainstem.

Two aspects of the trigeminal nerve, the large sensory root, and the smaller motor root, start from the ventrolateral aspect of the pons at its junction together with the middle cerebellar peduncle. The sensory root moves forward and laterally going over the apex of the petrous temporal bone and into the middle cranial fossa. Once over the apex of the petrous bone, the trigeminal or gassarion ganglion forms. Subarachnoid growth over this aspect of the trigeminal nerve is called Meckel's Cave.

Moving distally, the sensory portion of the surface of the ganglion supplies the origin to three large sections of the trigeminal nerve-the ophthalmic, maxillary, and mandibular roots. The sensory ophthalmic nerve originates from the anterolateral aspect of the ganglion and enters the lateral wall of the cavernous sinus, where it is located below the trochlear nerve.

In the cavernous sinus, it breaks up into three branches: the nasociliary, lacrimal and frontal. All these branches move into the orbit after exiting through the superior orbital fissure.

The sensory-only maxillary nerve originates from the gasserian ganglion. It enters the lateral wall of the cavernous sinus where it takes up the lowest position and then leaves the cavernous sinus, going into the pterygopalatine fossa via the foramen rotundum.

The largest section, the mandibular nerve, originates from the trigeminal ganglion and promptly enters the temple fossa via the foramen ovale. After appearing from the pons, the motor root of the trigeminal nerve moves forward and laterally, deep to the trigeminal ganglion's sensory root, and also enters the temple fossa via the foramen ovale. After appearing from the foramen ovale, it joins the mandibular nerve, and from there, the mandibular nerve includes both the motor and sensory fibers.

After exiting the skull, the ophthalmic nerve, which is purely sensory, enervates the upper third of the face, including the eyeballs, conjunctiva, the nasal cavity, the lacrimal gland, and the scalp up to the vertex. The ophthalmic nerve also forms the afferent aspect of the corneal reflex.

The purely sensory maxillary nerve innervates the middle third of the face, including most of the nasal cavity, upper teeth, and gums, the maxillary sinus, the mucous membrane of the pharynx, palate, and the dura mater of the middle cranial fossa. The maxillary nerve also conveys secretomotor fibers to the lacrimal gland and the glands of the palate, nose, and the oral cavity.

The mandibular branch is mixed: it's sensory nerves innervate the lower third of the face (except the small area over the angle of the mandible), including part of the auricle and the temple. The motor aspects of this large nerve innervate, as previously noted, the muscles of mastication, the mylohyoid, the anterior belly of the digastric muscle, the tensor palati, and the tensor tympani muscles. The mandibular nerve enables both limbs of the masticatory reflex.

## Trigeminal neuralgia

### *Epidemiology*

The prevalence of trigeminal neuralgia, which is reported, not the occurrence, is 0.16–0.3%.[3] The annual incidence of the disorder is reported to be 4-28/100,000 person years.[4] It has been reported to have a prevalence greater in femails than males with a female to male ratio of 3:2.[5]

The disorder has been reported to increase with age, with the typical mean age of onset being between 53–57 years of age.[6] However, trigeminal neuralgia can appear in children. A recent pediatric clinical study of 1040 patients found that 5 children had the disorder, their ages varying between 9.5 and 19.5 years of age.[7]

## Definition and classification of trigeminal neuralgia (TN)[8]

Trigeminal neuralgia is an oral-facial pain that is typically restricted to one or more divisions of the trigeminal nerve. Trigeminal neuralgia secondary to multiple sclerosis reflects a different pathophysiology as it appears to mostly be secondary to demyelinating lesions; TN in younger patients may be an early sign of later muscular sclerosis. In TN, the pain typically effects one side of the face. The pain occurs abruptly, and typically lasts a few seconds, two minutes maximally. While patients frequently report tha that their pain occurs spontaneiously, their pain paroxysms may be triggered by innocuous mechanical stimuli or movements often occur secondary to stimulation facial or intra-oral trigger zones.

Patients are typically pain free between the episodes of paroxysmal pain. If they do report more, or additional continuous pain in both the same distributions and the same periods as the paroxysmal pain, they are consider to have trigeminal neuralgia with concomitant continuous pain.

Trigeminal neuralgia is classified in three etiological categories:

Idiopathic trigeminal neuralgia occurs without apparent cause.

Classical trigeminal neuralgia is caused by vascular compression of the trigeminal nerve root.

Secondary trigeminal neuralgia is the result of a major neurological disease, such as a tumor of the cerebellopontine angle or multiple sclerosis or even a pontine ischemic infarction.

Either phenotype, that with purely paroxysmal pain or with concomitant continuous pain, may occur within any of the three categories.

Classical trigeminal neuralgia (TN) is the most common form, comprising about 75% of the cases. Using visualization via MRI with 5$^{th}$ cranial nerve protocols, patients can be found to have trigeminal neurovascular compression with ipsilateral morphological changes (distortion, indentation, atrophy of the nerve).[9]

About 15% of cases make up the secondary type which are associated with an underlying neurological disorder (not involving trigeminal neurovascular compression) including cerebellopontine angle tumor, arteriovenous malformation, pontine ischemic infarction and multiple sclerosis.[10]

Approximately 2% of patients with multiple sclerosis may have symptoms of TN, but they typically start earlier. The average age of TN in the general population is 53–57 YOA, while with MS, it can occur in patients over 40, and include between 4 and 6 people living with MS.[11,12]

About 10% of cases are idiopathic, showing no apparent cause of TN.

The Classical and idiopathic forms of TN are subclassified in groups with purely paroxysmal pain or with concomitant continuous pain (depending on the presence or absence of continuous or near continuous interictal pain).As noted by Di Stefano et al, concomitant continuous pain is typically associated with trigeminal nerve root atrophy.[13]

Classical TN is caused by neurovascular compression of the trigeminal nerve root by blood vessels in the posterior fossa in 80–90% of patients. The superior cerebellar artery (SCA) is the artery most often found to compress the trigeminal nerve root.other arteries can also be found compressing the trigeminal nerve root, including the anterior inferior cerebellar artery, the basal artery and an ectatic vertebral-basilar artery. The superior petrosal as well as the transverse pontine veins have also been found to cause neurovasular compression to the trigeminal nerve root.[14–17]

## Clinical features

The right side of the face is affected more often than the left ($R = 60\%$). It is rare for a patient to experience bilateral, simultaneous pain. A small percent of patients can experience pain that

changes sides (1.7–5%). If there is contralateral or bilateral, simultanous or side-alternating TN pain, the clinician must rule out an underlying neurological disorder.[18]

With a normal workup, idiopathic causes of constant or long-lasting bliteral TN pain can include: temporomandibular joint dysfunction, persistent idiopathic facial pain or even migraine with associated face pain.[6]

Patients with paroxysmal short-lasting pain need to be evaluated for a Trigeminal Autonomic Cephalalgia, particularly SUNA, especially if the pain is found to be predominantly in the V1 trigeminal distribution. TN pain most frequenctly affects the maxillary (V2) and mandibular (V3) division- only about 25% of cases have opthalmic distribution activity.[6,19]

The fre quency and duration of TN attacks can be variable. In 74% of patients, the pain lasts from less than a second to 2 min. A significant minority of patients document attacks that last 2–10 min. Seventy percent of patients may have a series of paroxysmal attackes that last up to an hour.[6]

In patients with long-lasting attacks (greater than 2 min), even with a phenotype consistent with TN, the clinician must still rule out other neurological diatheses.[20]

In general, the occurance of attacks, even in the same patients, can be significantly variable, and can range from a few attacks to several hundred attacks daily. About 40% of patients experience more than 10 attacks a day.[21]

In approximately two thirds of patients, TN has a relapsing/remitting pattern; there is a chronic pattern in the other third of patients.[6,20]

Remission periods vary a great deal and can last for months (37%) to years (63%).[20]

Trigger zones are a hallmark or pathognomonic feature of TN. These may be found setting off attacks by innocuous mechanical stimulation of the face as well as the intraoral mucosa ipsilateral to the side of the pain.[6,22]

Typical of TN, 91–99% if patients report triggered attacks. Patients typically report a mixture of both triggered and spontaneious attacks with 68–98% of patients having spontaneous attacks. If there is a total lack of triggered attacks, this should mandate the clinician to do a re=assessment of trigeminal autonomic cephalalgias (TACs) or craniofacial pathology[22,23].

The most potent trigger is light tactie stimulation, while painful and thermal stimulation is typically ineffective at eliciting pain in TN.[23]

Common triggers include light touch, water in a shower, breezes from open windows in a moving car, talking, chewing, brushing the teeth, washing or drying the face, drinking and shaving.[23–25]

The majority of patients have multiple trigger zones. The trigger zone location is not necessarily in the zone of pain (i.e. an intraoral trigger zone inducing maxillary region pain.[23,24]

There are multiple areas both intra and extra-orally in which trigger zones can be found. It can be fairly easy to recognize an extra-oral trigger zone, but intra-oral trigger zones are more difficult even for the patient to identify- they know that touching an area of their gum or even a tooth can stimulate a paroxysmal pain; but chewing and talking which can presage a electivcal-like jolt, make it difficult to identify a specific intra-oral trigger zone.[24]

The most common activities of daily living that act as trigger maneuvers in 120 patients with Classical Trigeminal Neuralgia include (in decesending order of number and percent of patients effected): talking (71–58%); washing the face (52–43%); chewing (49–41%); brushing the teeth 43–36%); drying the face (43–36%); eating (23–19%); drinking (17–14%); shaving (16–13%); applying makeup (7-,6%); combing the hair (2-2%) and washing the hair (2-2%).[24]

Specific movements in the same group of 120 patients with Classical Trigeminal Neuralgia that induce or trigger TN (in descending order of number and percent of patients): swallowing (13(11%); blowing the nose (11–9%); gently touching the face (the act with the majority of patients) (106–88%); jaw movement (7-6%), head movement 7-6%); yawning (7-6%); flexing the trunk forward 5-4%); pronouncing labial letters (5-4%); raising the voice (5-4%); laughing (3-3%); eye movement (2-2%) and tongue movement (2-2%).[24]

A refractory period, or a period of seconds to minutes during which time another attack can not be provoked can occur after a TN attack is triggered. In the TACs, particularly Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing

(SUNCT) and Short-lasting Unilateral Neuralgiform headache attacks with Cranial Autonomic Symptoms (SUNA) most typically have no refractory period after exposure to a trigger- the attacks can occur immediately after another attack, and 300 hundred attacks in an hour are possible.[26,27]

It is not typically recognized, but TN may have associated cranial autonomic symptoms. Rasmussen described 98 out of 229 (43%) of patients in whom pain was accompanied by facial autonomic symptoms: Lacrimation (31%); rhinorrhoea (9%); hypersalivation (7%) and facial swelling/flushing (5%).[28]

Another study reported 48 of 158 patients (31%) endured ipsilateral TACs.[6]

In both series, the symptoms were more likely to occur in the V1 distribution.

Sjaastad et.al. looked at the phenotype of 19 patients with V1 TN and noted lacrimation (42%), conjunctival injection (16%) and rhinorrhoea (11%) but the Cranial Autonomic Symptoms were mild in all patients.[29]

Lambru et.al. looked at a series reporting TN patients with cranial autonomic symptoms and found that they were misdiagnosed cases of SUNA. These were the trigeminal autonomic cephalalgias (TACs) including both SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) in patients with both conjunctival injection and tearing and SUNA- (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms) in patients with at least one cranial autonomic symptom but not both conjunctival injection and tearing.[32,33]

In a patient with a TN phenotype who only has mild and sporadic crantial autonomic symptoms, the diagnosis of TN should be maintained. However, if the autonomic symptoms are severe or intense (i.e., produce lacrimation and rhinorrhoea) numerous (>1 of these symptoms) and it consistently accompanying most attacks, then the patient should be diagnosed with either SUNCT or SUNA. The diagnosis of SUNA more likely than TN includes clinical features that show predominant pain in the V1 trigeminal distribution, spontaneous-only attacks, absence of a refractory period in triggered attacks and longer lasting attacks.[30,31]

Fourteen percent to 50% of patients with TN have concomitant continuous or near continuous pain. TN with concomitant continuous pain appears to be pathophysiologically different in that it responds less well to treatment vs. the purely paroxysmal form.[13]

Stuides have shown that the concomitant continuous pain develops with or possibly even before the onset of paroxysmal pain. TN with Pain or Concomitant Continuous Pain is more prevalent in women, more often associated with sensory abnormalities than paroxysmal TN. Abnormal blink reflexes and pain-related evoked potentials have been seen in various studies, which are thought to indicate an overactivation of central sensory transmission. In TN with Concomitant Continuous Pain, it was found that the trigeminal nerve root was more severely atrophic- with axonal loss and abnormal activity in denervated trigeminal second order neurons is postulated. This is not seen in Classical TN.[13,18,33]

Both the neurological and general physical examinations are typically within normal limits. However, approximately 30% of patients may have sensory changes including mild hypoesthesia. Also, in some patients, during a severe attack, the pain can evoke ipsilateral facial muscle contraction (tic douloureux).

## Pathophysiology

Classical TN has been found to be secondary to proximal neurovascular compression of the trigeminal sensory root near the brainstem (the root entry zone) adjacent to a blood vessel, artery or vein. The root entry zone is felt to be an area that is vulnerable to demyelination due to its transition from the peripheral Schwann cell myelin sheath to central myelin generated by oligodendroglia.[34]

The vascular compression may begin a process of focal demyelination and remyelination, possibly mediated by microvascular ischemic damage. The excitability threshold of affected

fibers can be lowered by these changes, and they would promote imapprorpate ephaptic propagation towards adjacent fibers.[34,35]

Tactile signals from fast myelinated (A$\beta$) fibers can directly activate the slow nociceptive (A$\delta$) fibers, which would cause the high-frequency paroxysms that are characteristic of TN. After a few seconds, these repetitive dischares spontaneiously run out and then the refractory period, a brief period of inactivity, occurs, where triggering actions will not provoke pain.[36,37]

The ignition hypothesis: vascular compression leads to axotomized somata which become hyperexcitable, leading to paroxysmal nociceptive transmission.[38]

The effectiveness of sodium channel blockers suggests that there is an abnormal expression of voltage-gated sodium channels in both Classical and Idiopathic TN-sodium channelopathies. In TN, Nav. 1.7, Nav 1.3 and Nav. 1.8 were found to be abnormally expressed and they could possibly be responsible for rapid activation and inactivation as well as maintenance of the action potential.[39]

Hypersensitivity of tactile A-$\beta$ fibers may, over time, lead to sensitization of second order wide dynamic range (WDR) neurons in Lamina V of the dorsal horns and trigeminal nuclei. Information of tactile A-$\beta$, as well as nociceptive A-$\delta$ and C fibers all converge on the WDR neurons and their sensitization may promote the perception of pain secondary to cutaneious stimulation.[40]

## Differential diagnosis

As noted above, TN, per the ICHD-3 has recurrent paroxysms of unilateral facial pain in the distrubtion of one or more divisions of the trigeminal nerve, which lasts a fraction of a second to two minutes and it is severe and electrical-shock like, shooting, stabbing or sharp in quality and can be precipitated by innocuous stimuli both with the affected trigeminal dermatorme or not.[1]

A thorough history and neurological examination is essential for achieving the diagnosis. Yet, the differential diagnosis is wide, with at least 5 other problems that can be involved, with other neuropathic and neuralgiform headache as well as oro-facial pain problems.

One of the most obvious etiologies to consider are the dental and other facial pain issues:[41]
Dental causes:

Dental caries
Pulpitis
Dental sensitivity
Periodontal disorders
Pericoronitis
Cracked tooth
Alveolar osteitis

Sinus causes:

Salivary stone

Temporomanibular joint causes:

Temperomandibular disorders

There are then the other neurological disorders that may contribute to the pain:
Neuropathic pain:

Glossophayngeal neuralgia
Nervus intermedius neuralgia
Post-herpetic neuralgia
Painful trigeminal neuropathies

Atypical odontalgia
Burning mouth syndrome

Trigeminal autonomic cephalalgias:

SUNCT (Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)
SUNA (Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms)
Cluster headache
Hemicrania continua

Other:

Persistent idiopathic facial pain (PIFP) (See below)
Primary stabbing headache

## Diagnostic algorithm

Consideration for an appropriate algorithm to diagnose TN is presented in the following discussion.

First, a patient must have unilateral facial pain that is electrical-like, and fits the ICHS-3 diagnostic criteria.[1]

Next, the patient must have a history of not only paroxysms of pain, but also pain distribution within the facial or intraoral trigeminal nerve territory. This means just that- the pain does not extend to the posterior third of the scalp (cervical nerve territory), nor does it extent to the posterior part of the external ear or the angle of the mandible.

If neither of these two conditions are present, it is unlikely that the patient has TN. If these aspects are true, it is more probable that the patient has possible TN or neuropathic pain.

Unilaterality of the pain is also typical of TN. In patients with multiple sclerosis (MS), they may experience pain on both sides of the face during the disease, but they don't present with simulataneous bilateral pain. Trigeminal neuralgia may be a premonitory sign of multiple sclerosis, with young people developing Multiple Sclerosis before being diagnosed with MS. In one study, 15% of people had TN before being diagnosed with MS. The risk of TN is 20 times higher in patients with MS than in the general population. The prevalence of TN in patients with is between 1.9 and 6.3%.[42–44]

If the paroxysmal pain is triggered by a typical maneuver as noted above- touching a facial or intraoral trigger zone, talking, chewing, brushing their teeth, is it very possible that the patient has clinically established TN.

It is not totally unusual to see a man come to the office with only a half of his face shaved, or a woman with only a half of her face with makeup.

Also, when a patient with TN also has muscle contractions associated with the pain, forinstance, pulling the ipsilateral side of the mouth up, that would be what has been known as "tic douleroux".

Next, after a clinical diagnosis, typically an MRI with a fifth cranial nerve protocol that looks carefully at the trigeminal nerve root is done. If the MRI shows a vascular compression, either by an artery or vein, that would yield a diagnosis of Classical TN, where Idiopathic TN shows no compression. If the study should show other forms of neurological disease such as a tumor of the cerebellopintine angle or multiple sclerosis, this would be indicative of Secondary TN.

When an etiology has been established, or when it hasn't (and a diagnosis of definatie neuropathic pain is made), you have either Classical TN, with an MRI showing neurovascular compression with morphological changes secondary to this compression of the trigeminal nerve root. If the MRI demonstrates major neurological disease, you have Secondary TN. The diagnosis of Idiopathic TN is secondary to a negative MRI. Still, neurosurgically, a microvascular decompression may still be attempted, as vascular compression may still be found.

## Back to the trigeminal autonomic cephalalgias (TACs)

SUNCT (Short- lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and SUNA (Short- lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms) are the only two TACs which are induced by innocuous stimulation within the trigeminal distribution. Studies have demonstrated that demographics and clinical phenotypes of SUNCT and SUNA have a significant overlap with TN.[45]

A recent cross-sectional MRI study of 159 patients with SUNCT or SUNA showed that a significantly higher proportion of neurovascular contact with morphological changes in the syumptomatic trigeminal nerves, comprarted to asymptomatic nerves was found. Specifically, multivariate analysis of radiological predictors associated with the symptomatic side indicated the presence of neurovascular contact with morphological changes was strongly associated with ipsilateral pain. It was postulated that this finding may be a shrared causative factor associated with TN.[46]

Another recent large, prospective open-label study in 161 patients on the medical treatment of SUNCT/SUNA showed that the efficacy of sodium channel blockers was good, therefore showing a therapeutic overlap with TN.[47]

All-together, this evidence suggested that SUNCT and SUNA and TN may constitute a continuum of the same disorder.[48]

Lambru, et.al., in a new paper,[49] goes over the differences between TN and the TACs, SUNCT/SUNA. The most significant are: In TN, the most prominent pain distribution is V2,V3> V1. In SUNCT/SUNA it is V2 and V3; The duration of TN is <1–120 seconds, while the pain of SUNCT/SUNA is 1-600 seconds; Autonomic features are prominent in the TACs, but none or sparce in TN. There is a refractory period in TN, but not in the TACs. Finally, the preventative treatment of choice of TN is a sodium channel blocker (see below) while for the TACs, it is lamotrigine.

## A treatment algorithm

After going through a possible treatment algorithm, a presentation of each individual aspect of treatment is provided.

Generally speaking, the first form of treatment is pharmacotherapeutic management. As we discussed above, there are three forms of TN- Classical, Idiopathic and Secondary.

Treatment of Classical TN, the most common form: Following the diagnosis, one can look at 3 groups of agents for TN treatment. The most common and typically most effective include carbamazepine or oxcarbazepine, both anticonvulstant sodium channel blockers. It must be remembered that carbamazepine by hepatic autoinduction will achiefe steady state in 3 to 5 weeks following a fixed dose schedule during this time period. If these medications are not helpful, a therapeutic trial of lamotrigine and gabapentinoids can be trialed- gabapentin or pregabalin. The therapeutic trials are facilitated in a patient, patient centered, patient focused personalized treatment plan utilizing renal, hepatic, neurologicial events with a complete metabolic profile and other testing required by product labeling for monitoring and dosing parameters. The patient and other concerned parties may be given thorough information of the pharmacotherapies.

If the medications are either not successful or the patient gets to maximum dosages, typically over time, the next treatment would be neurosurgical, the trigeminal microvascular decompression (MVD). MVD is the primary surgical procedure performed when we have seen vascular compression of the trigeminal nerve root- in both Classical TN as well as idiopathic TN.

If, after MVD, patients may need medications and the sodium channel blockers have not been tried, they should be here. Other medications to trial may include botulinum toxin type A, ba-

clofen and others, including low dose naltrexone (by virtue of clinical treatment, not per a RCT at this time).

If pain returns after a MVD and these medications, there are other forms of treatment. Through radiation oncology, Gamma Knife (cyberknife) Surgery is typically considered first. Other more interventional techniques would include radiofrequency thermocoagulation, balloon compression and glycerol rhizolysis. Internal neurolysis can be considered, but the author has seen two patients with anesthesia dolorosa when this is performed after a MVD.

In patients with Idiopathic TN, the same medications noted above would be used first: the sodium channel blockers carbamazepine or oxcarbazepine; lamotrigine; the gabapentinoids; botulinum toxin type A; and baclofen. If the patient maxes out the medication dosages and still has pain, further treatment may include a trigeminal MVD. The other noted treatments may also be considered: a gamma knife surgery, radiofrequency thermocoagulation, glycerol rhizolysis, internal neurlysis and ballon compression.

In patients with Secondary TN, it is impreitive that the underlying cause be treated. This this does not stop the TN symptoms, then the medications noted above would be used: carbamazepine, oxcarbazepine, lamotrigine, the gabapentinoids; baclofen or botulinum toxin type A. If the medications do not help, in spite of the patient maxing out the medication dosages, after the underlying condition of secondary TN has been treated appropriately, one can conisser the surgical procedures (trigeminal MVD or gamma knife surgery) or the more interventional procedures, glycerol rhizolysis, radiofrequency thermocoagulation, or balloon compression. Per Lambru et.al.[49] consider MVD if the secondary cause is optimally treated, and one finds evidence of neurovasular compression of the trigeminal nerve root. Caution should be used in MS with ipsilateral pontine plaque.

## Treatment

### Pharmacotherapy

Carbamazepine and Oxcarbazepine (Anticonvulsants, sodium channel blockers)

Sodium channelopathies, with abnormal expressions of Nav. 1.7, Nav 1.3 and Nav 1.8 are found in TN and make these sodium channel blockers the primary medications: carbamazepine (neuronal voltage-gated Na+ channel blocker) and oxcarbazepine (Sodium channel inhibitor).

Carbamazepine, can be given 200-1200 mg a day in two or three doses and is very effective with a 60–100% response rate. It has many AEs, and patients may have a difficult time adjusting to them: drowsiness, cognitive impairment, dizziness, ataxia and rash, as well as possible aplastic anemia. Serial labs are needed to assess for leukopenia, liver injury and hematologic toxicity. Testing for HLA-B*1502 in patients of Asian descent is important.- it significantly increases the risk of Steven-Johnson syndrome in these patients (in Han Chinese); for the Steven-Johnson Syndrome and toxic epidermal necrolysis.[50,51,53,55]

Carbamazapine has multiple drug interactions- it is a potent inducer of multiple cytochrome P-450 hepatic oxidases, including CYP3A4, CYP1A2 and CYP2C9. Contraindications include tricyclic antidepressants, monoamine oxidase inhibitor. It's use includes: NNT=2, NNH-3 for minor side effects, and for major side effects. Finally, carbamazepine has an approximately 50% failure rate over 10 years.[51,53,58]

In some ways, Oxcarbazepine is much better tolerated and much easier to titrate (using 150 mg capsules, with a max dose of 2400 mg). Symptomatic hyponatremia is not uncommonly seen: there is a lower frequency of carbamazepine-like AEs. Oxcarbazepine exerts anti-TN effects similar to carbamazepine. The response rate can also go up to 100%. Severe side effects are less pronounced with oxcarbazepine compared to carbamazepine, particularly rash. When prescribing oxcarbazepine in patients who have developed rash on carbamazepine, the risk of cross-allergy is about 25%. Oxcarbazepine may cause hyponatremia more frequently than carbamazepine. Eslicarbazepine is increasingly used as an alternative to carbamazepine and oxcarbazepine as an anticonvulsant. Eslicarbazepine has been used in multiple sclerosis patients to treat refractory trigeminal neuralgia, as it is also a sodium channel blocker.[50–54,73]

Extended release oxcarbazepine may also be used once the appropriate dose of oxcarbazepine has been obtained. Lacosamide, also an sodium channel drug has also been used in patients who can not tolerate oxcarbazepine or carbamazepine. (A case report[250] was found, but not an RCT).

For patients who can not tolerate carbazazepine or oxcarbamazepine, Lamotrigine can be a helpful add-on therapy. Titration is slow. Ten percent can develop benign adverse cutaneous reactions; however, Steven Johnson Syndrome is rare.[56]

There are 15 gabapentin trials, however they are perfomed in China with poorly noted inclusion criteria, endpoints and dosages. One small trial with pregabaline is found.[57]

A new medication in development, Vixotrigine, has a mechanism of action as a Nav 1.7 voltage gated sodium channel inhibitors. They are apparently in Phase III at this time. They have published the design of the Phase III studies for the treatment of trigeminal neuralgia. They are testing patients with Classical TN.[210]

Baclofen may be helpful in patients with multiple sclerosis who may be using the medication for spacticity.[58]

The efficacy of onabotulinumtoxinA is inconsistent. Doses in the range of 25–100 Units following the pain, 1 cm apart for a total of 10–20 injections is superior to placebo, with responders 68–86% vs. placebo 15–32%.[59]

It would appear that OnabotulinumtoxinA (BTxA) acts at both peripheral and central sites. Peripehrally, it blocks the docking of intraneuronal vesicles to the inner membrane of nerve termals inhibiting the release of neuropeptides and neurotransmitters. There are decreases of extracellulater concentrations of ACH (adrenal cortical hormone), substance P, 5-HT (serotonin), CGRP (calcitonin gene related peptide), glutamate and proinflammatory mediators. Plasma CGRP levels decrease in TN patients who respond to BTxA.[59,60]

Centrally, BTxA acts at the level of the spinal dorsal horn secondary to retrograne toxin transport. Micoglial activation is diminished and inhibition of the sodium ion channel activity occurs.[61–63]

## Treating TN in the elderly[64]

Not uncommonly, one sees elderly patients (>65 YOA) with TN. This makes it encumbant on the practitioner to pay special attention to other medical issues.

When one sees a patient with Classical TN (based on history, neurological examination and MRI or CT if secondary TN is suspected, and a neurovascular compression of the trigeminal nerve root is found – utilizing a Vth cranial nerve protocol on MRI, one would want to obtain a baseline electrocardiogram, CBC with differential, liver function studies and electrolytes.

Many would start the patient on carbamazepine (CBZ) 100 mg, increase up to 600 mg-1200 mg a day in 3 or 4 doses. You would want to use the lowest dose possible for maintenance.

The author would utilize oxcarbazepine from the start instead of using carbamazepine first. The AEs from that medication would typically make it necessary to move to oxcarbazepine anyway. Also, oxcarbazepine allows better and easier titration than carbamazepine, and a wider spread of medication dosages.

In patients with atrioventricular (AV) blockade, they should be excluded from the use of carbamazepine, and you should do a HLA-B 1502 screen on patients from the East or Southeast Asia. These patients should be placed on oxcarbazepine (OXC) for these medical reasons, starting OXC at 150 mg, and increasing slowly up to 600 mg to 1800 mg in 3 doses a day. As always, the lowest dose that relieves the patients' pain should be used for maintenance.

If the use of CBZ or OXC had good effect, one would perform regular checks for skin rash, complete blood counts (esp. for CBZ) and electrolytes (especially on patients on diuretics) and liver function panels. Also, sodium wasting is a not-uncommon AE of OXC and must be continually re-evaluated.

If the medication has no effect or has side effects that the patients' can't tolerate, then consider second line treatmens, either substitureing or adding on Lamotrigine or Baclofen or even lacosamide.

## Other medication choices

Amitriptyline 12.5 to 25 mg BID with pregabalin 75 mg BID gave TN pain relief in 3 female patients (ages 39,50 and 84) after treatment failure with CBZ.[65]

The author has received 5 female patients (ages 50–72) with Classical or Idiopathbic TN who were taking between 3 mg and 6 mg of Low Dose Naltrexone (LDN) and swore it stopped their pain.

The author has since used LDN 1.5 mg capsules (made in compounding pharmacies) in dosages of 4.5 yo 6 mg, with good results when supplementing OXC. The patients were asked to take the medication 3,4 h prior to sleep to prevent very vivid dreams.

One study shows LDN in a rat model of TN which stopped their pain. There were two groups- Carbamazepine and LDN- 14 days after surgery, the first dose of LDN or carbamazepine partially reversed facial allodynia. After 10 days of treatment, both drugs completely reversed facial allodynia. The LDN did have an effect on inflammatory biomarkers in the CNS including TNF-alpha, BDNF, IL-10 and toll-like receptor-4.[66–68]

## Acute exacerbation[69–72]

In the case of severe acute exacerbations of TN, there are several ways to consider managing this problem.

First would be to use an intravenous bolus of fosphenytoin 15–20 mg/kg. You can use 2 mg/kg/min or 150 mg/min. Possible AEs: cardiac conduction blocks, hypersensitivity rash, headache, nystagmus, drowsiness and fatigue.

The other alternative is intravenous lidocaine 5 mg/kg bolus. It would be given 5 mg/kg continuous infusion over an hour. Significant AEs: cardiac depression, hyptension and arrythmias.

To perform either mediation use, CONTINUOUS CARDIAC MONITORING IS A MUST!

A history of ventricular arrhythmias is a contraindication.

One would typically want to perform this in a safe area, such as an ICU in case of a significant AE. It may be tried in other infusion centers with appropriate cardiac monitoring and the ability to handle an acute cardiac AE.

## Be nice to the patient!

TN induces a significant decrement on a patients' quality of life (QOL). The author is therefore surprised to see the number of patients with TN who have never been given simple remedies to help their QOL.

First, one can use viscous lidocaine 2%, 15 ml, as a mouthwash- have the patient swish for 30 s and then spit it out, every 3 h as needed. This numbs the mouth but at the same time, it can relieve, in patients with intra-oral trigger zones, those patients who get increased TN with eating, chewing, brushing their teeth, even patients with TN from talking or swallowing (some of my patients do "gargle" with it, but not swallow it). Patients are appreciative of being able to have a meal without worry of increased TN.

Always warn the patient that they must be very careful- as they may bite their tongue, inner cheeks or lips when their mouth is numb, they must be warned to be careful. After a while it becomes second nature to them.

**Table 1**
Summary of RCTs for pharmacotherapeutic treatments in TN

| | Number of RCTs | Number of patients | Dose range (mg/day) | Responder rate |
|---|---|---|---|---|
| Carbamazepine | 3 | 138 | 800–1200 | 68%–100% |
| Oxcarbazepine | 1 | 48 | 600–1800 | 100% |
| Lamotrigine | 1 | 14 | 200–400 | 85% |
| Gabapentin* | 16 | 1156 | Up to 3600 | Reportedly similar to carbamazepine |
| Baclofen | 1 | 10 | 30–60 | 70% |
| Botulinum toxin type A | 4 | 178 | 25–100 units | 68%–86% |
| Pimozide | 1 | 48 | 4–12 | 100%† |
| Tizanidine | 1 | 12 | 18 | 20% |

Pregabalin: no RCTs available.
*Gabapentin: all RCTs are in Chinese language and results difficult to access.
†Pimozide trial has been heavily criticised for methodological pitfalls.
RCTs, randomised controlled trials.

Note that there are not large numbers of either patients or RCT (randomized, controlled trials) for the use of specific medications for TN. Also note the issue re: gabapentin, as noted above.

Another thing that is very helpful is to desensitize the patients' trigger zones on their face. One can do this by alternatating, Q6 h, diclofenac gel 1%, now over the counter- apply using the measured applicator device as 1-2 grams onto the trigger zones- alternating every 6 h with lidocaine gel 4 or 5%, while awake. After 3-4 weeks, there is a major decrement in facial trigger zone activity, and the patients are very relieved.

## Pharmacotherapeutic treatments

It is interesting to see the RCTs that the medication management of TN is based on. Note that there are few trials that have significant patient numbers.

Table 1 is from Lambru.[74]

## Treatment: surgical and interventional

Prior to the development of the Janetta procedure by Peter Janetta in 1963, the treatment for TN was removal of part or more of the Gassarian Ganlion. The following Fig. 1 is an article from 1907 talking about the "technique".

The major discussion dwelt around the Hartley-Krause operation for removal of the Gassarian ganglion. The significant neurological issues secondary to this are self-evident.

No authorship is noted in Fig. 1 just the journal, The Hospital, November 16, 1907. (This author found these on the web years ago and can not find them again at this time.)

Surgical treatments are reserved for patients with TN that are refractory to medication management.

There are three types of surgical interventions:

The first is invasive, non-ablative and is most usually performed- microvascular decompression.

The second is non-invasive ablative, using stereotactic radiosurgery (gamma knife, or cyber knife) which focuses radiation at the trigeminal root entry zones.

The third consists of invasive, ablative and controlled lesioning of the trigeminal ganglion or root by: mechanical means (balloon compression); thermal means (radiofrequency ther-

# POINTS IN SURGERY.

## TRIGEMINAL NEURALGIA AND ITS SURGICAL TREATMENT.

TRIGEMINAL neuralgia is an affection which is characterised by the occurrence of paroxysms of pain in the area of distribution of the fifth cranial nerve. The age or sex of the patient does not seem to have any relation to the frequency of the complaint, although some authorities state that it is most commonly met with in middle-aged men. The pain, which is appallingly severe, comes on in paroxysms. At first the attack lasts only for a short time—sometimes as short as a few seconds—and there is an interval of days, or even weeks, before a second one supervenes; but as the disease progresses the paroxysms become prolonged and the intervals between them become shortened, so that the patient has little or no freedom from his agony, and eventually his life becomes a burden to him. The attacks seem in any given case to start in some branch of the fifth nerve which is constant, most commonly the maxillary division. The pain, however, spreads from that division to adjacent areas, and in advanced cases not only the whole distribution of the fifth nerve may be picked out, but the nerves supplying the adjacent areas of the neck and face may become involved. During the attack the patient presents a picture of extreme misery. The muscles of his face, and sometimes of his neck also, are subject to involuntary spasms, and he is constantly shifting his head into some new position in the hope that this may bring him ease. Counter-irritation seems to afford some relief, and to this end he presses on and rubs the affected area with his hand. But when the paroxysm has passed away the opposite is the case, and now the slightest stimulus appears sufficient to bring on another bout of pain. Eating, or even talking, may be sufficient to do this, and he therefore keeps himself absolutely still. On examination it will be found that certain localised areas are tender on pressure, and that these correspond generally to the points of emergence of the branches of the fifth nerve from their bony foramina.

### TWO DISTINCT CLASSES.

Cases of trigeminal neuralgia may be divided into two distinct classes: (i.) Those in which some local focus of irritation can be found, and (ii.) those in which no organic cause can be detected. In the first class there can be no question that dental caries is the most common of such foci, particularly caries of one of the upper molars. In one recorded case the neuralgia was caused, not apparently by caries, but by the pressure of a metal stopping, which was separated from the nerve pulp by only a thin shale of bone. The medical man may be misled into overlooking dental caries by the fact that the pain is often referred at first to some tooth other than the carious one. Other causes which may lead to trigeminal neuralgia are abnormal conditions of the nose and of the eye. Among the former, rhinitis, nasal polypi, and suppuration in one of the accessory sinuses must be looked for; while, among ophthalmic causes, uncorrected errors of refraction account for a small percentage of the cases. But there is, as has been said, a second class of case, in which no such cause can be found, and there is no diseased condition of the nerve itself or of its nuclei to account for the symptoms. In the days when the Gasserian ganglion was first removed for this complaint it was thought that a microscopical examination of the tissue removed would demonstrate the presence of an inflammatory change in the trunks of the nerve or its nuclei. This is not, however, the case. In nearly all cases the ganglia which are removed are found to appear normal under the microscope. The cases in which some organic cause can be found are more easy to treat, for if the local focus be dealt with by suitable measures, as, for instance, the removal of a carious tooth or a nasal polypus, or the correction of any errors of refraction, the neuralgia tends to disappear. But in the primary, or so-called idiopathic cases, in which no apparent cause can be found, the disease tends to progress steadily in spite of medical treatment. What usually happens is that the patient rings the changes on the more ordinary antispasmodic drugs, such as phenacetin, antipyrine, and antifebrin, until he finds which one of them gives him most relief, and he takes increasing doses of this, until it loses its power to allay his pain; and finally he finds that the only drug that gives him any real comfort is morphia.

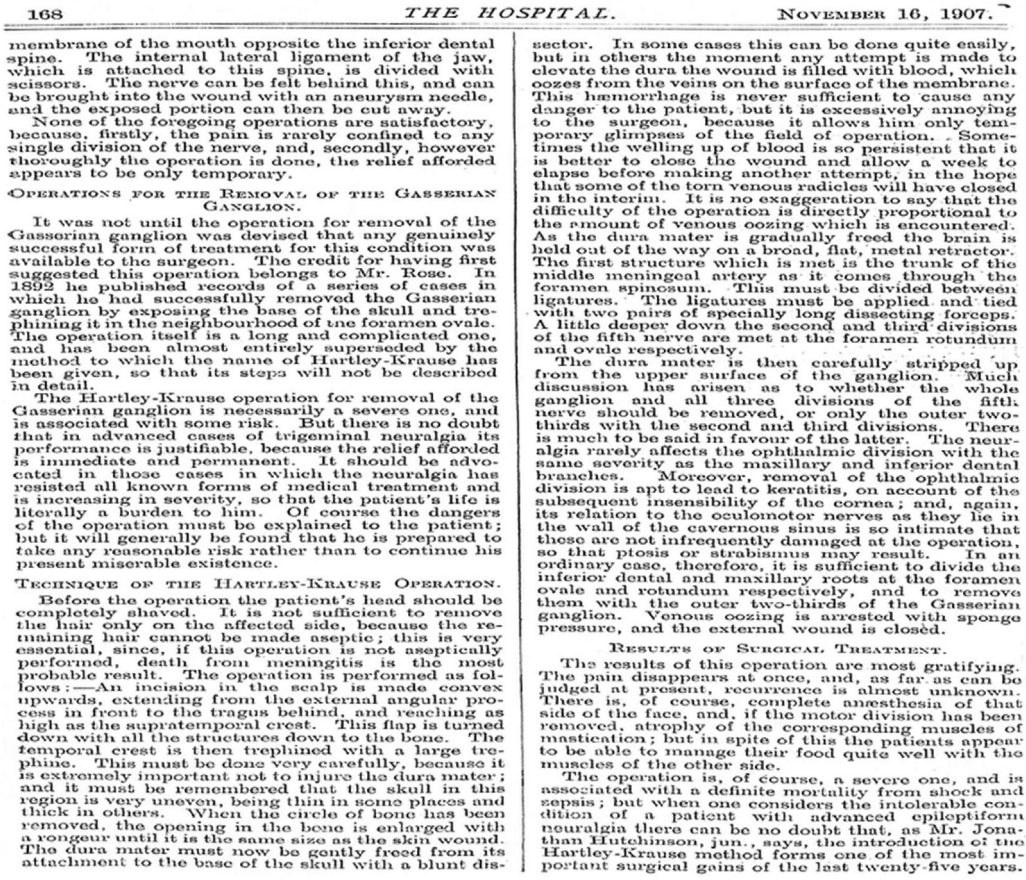
### SURGICAL TREATMENT.

The following methods of surgical interference have been devised from time to time in the hope of giving relief in these distressing cases:—(i.) Supra-orbital neurectomy. The nerve trunk is exposed through a small incision in the line of the eyebrow as it emerges through the supraorbital notch. It is pulled up, and as much as possible of the nerve trunk is removed. The disadvantage of the operation is that the neuralgia is rarely, if ever, confined to the supraorbital division, and, even if it is, the relief afforded by a simple neurectomy is not likely to be permanent.

(ii.) Infraorbital neurectomy. A short incision is made along the natural fold of the cheek over the infraorbital foramen. The nerve is seized as it emerges and pulled out as far as possible. In most cases no improvement results, because the dental branches are not removed by this procedure. To overcome this objection a more radical operation was devised. A V-shaped incision is made in the skin of the cheek, and a portion of the anterior wall of the antrum of Highmore is taken away with a chisel. The floor of the infraorbital foramen is removed, and the infraorbital nerve can be torn out entire from its attachment posteriorly.

(iii.) Neurectomy of the inferior dental nerve. This is done by making an incision in the mucous

**Fig. 1.** A year 1907 article reflecting TN and the corresponding surgical technique over 100 years in the past by unknown authorship.



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membrane of the mouth opposite the inferior dental spine. The internal lateral ligament of the jaw, which is attached to this spine, is divided with scissors. The nerve can be felt behind this, and can be brought into the wound with an aneurysm needle, and the exposed portion can then be cut away.

None of the foregoing operations are satisfactory, because, firstly, the pain is rarely confined to any single division of the nerve, and, secondly, however thoroughly the operation is done, the relief afforded appears to be only temporary.

OPERATIONS FOR THE REMOVAL OF THE GASSERIAN GANGLION.

It was not until the operation for removal of the Gasserian ganglion was devised that any genuinely successful form of treatment for this condition was available to the surgeon. The credit for having first suggested this operation belongs to Mr. Rose. In 1892 he published records of a series of cases in which he had successfully removed the Gasserian ganglion by exposing the base of the skull and trephining it in the neighbourhood of the foramen ovale. The operation itself is a long and complicated one, and has been almost entirely superseded by the method to which the name of Hartley-Krause has been given, so that its steps will not be described in detail.

The Hartley-Krause operation for removal of the Gasserian ganglion is necessarily a severe one, and is associated with some risk. But there is no doubt that in advanced cases of trigeminal neuralgia its performance is justifiable, because the relief afforded is immediate and permanent. It should be advocated in those cases in which the neuralgia has resisted all known forms of medical treatment and is increasing in severity, so that the patient's life is literally a burden to him. Of course the dangers of the operation must be explained to the patient; but it will generally be found that he is prepared to take any reasonable risk rather than to continue his present miserable existence.

TECHNIQUE OF THE HARTLEY-KRAUSE OPERATION.

Before the operation the patient's head should be completely shaved. It is not sufficient to remove the hair only on the affected side, because the remaining hair cannot be made aseptic; this is very essential, since, if this operation is not aseptically performed, death from meningitis is the most probable result. The operation is performed as follows:—An incision in the scalp is made convex upwards, extending from the external angular process in front to the tragus behind, and reaching as high as the supratemporal crest. This flap is turned down with all the structures down to the bone. The temporal crest is then trephined with a large trephine. This must be done very carefully, because it is extremely important not to injure the dura mater; and it must be remembered that the skull in this region is very uneven, being thin in some places and thick in others. When the circle of bone has been removed, the opening in the bone is enlarged with a rongeur until it is the same size as the skin wound. The dura mater must now be gently freed from its attachment to the base of the skull with a blunt dissector. In some cases this can be done quite easily, but in others the moment any attempt is made to elevate the dura the wound is filled with blood, which oozes from the veins on the surface of the membrane. This hæmorrhage is never sufficient to cause any danger to the patient, but it is excessively annoying to the surgeon, because it allows him only temporary glimpses of the field of operation. Sometimes the welling up of blood is so persistent that it is better to close the wound and allow a week to elapse before making another attempt, in the hope that some of the torn venous radicles will have closed in the interim. It is no exaggeration to say that the difficulty of the operation is directly proportional to the amount of venous oozing which is encountered. As the dura mater is gradually freed the brain is held out of the way on a broad, flat, metal retractor. The first structure which is met is the trunk of the middle meningeal artery as it comes through the foramen spinosum. This must be divided between ligatures. The ligatures must be applied and tied with two pairs of specially long dissecting forceps. A little deeper down the second and third divisions of the fifth nerve are met at the foramen rotundum and ovale respectively.

The dura mater is then carefully stripped up from the upper surface of the ganglion. Much discussion has arisen as to whether the whole ganglion and all three divisions of the fifth nerve should be removed, or only the outer two-thirds with the second and third divisions. There is much to be said in favour of the latter. The neuralgia rarely affects the ophthalmic division with the same severity as the maxillary and inferior dental branches. Moreover, removal of the ophthalmic division is apt to lead to keratitis, on account of the subsequent insensibility of the cornea; and, again, its relation to the oculomotor nerves as they lie in the wall of the cavernous sinus is so intimate that these are not infrequently damaged at the operation, so that ptosis or strabismus may result. In an ordinary case, therefore, it is sufficient to divide the inferior dental and maxillary roots at the foramen ovale and rotundum respectively, and to remove them with the outer two-thirds of the Gasserian ganglion. Venous oozing is arrested with sponge pressure, and the external wound is closed.

RESULTS OF SURGICAL TREATMENT.

The results of this operation are most gratifying. The pain disappears at once, and, as far as can be judged at present, recurrence is almost unknown. There is, of course, complete anæsthesia of that side of the face, and, if the motor division has been removed, atrophy of the corresponding muscles of mastication; but in spite of this the patients appear to be able to manage their food quite well with the muscles of the other side.

The operation is, of course, a severe one, and is associated with a definite mortality from shock and sepsis; but when one considers the intolerable condition of a patient with advanced epileptiform neuralgia there can be no doubt that, as Mr. Jonathan Hutchinson, jun., says, the introduction of the Hartley-Krause method forms one of the most important surgical gains of the last twenty-five years.

**Fig. 1.** Continued

mocoagulation; chemical means (glycerol rhizolysis) and separation of the trigeminal fascicles in the posterior fossa (internal neurolysis).

## Microvascular decompression (MVD)

This procedure is the first choice surgery in patients with Classical TN. The surgery involves separating the offending vessel which was inducing neurovascular compression, typically the superior cerebellar artery, from the nerve, by transposing it and placing a Teflon (polytetrafluoroethylene) pledget between the nerve and the artery. The surgeon can also use slings to the tentorium that can cradle the artery away from the trigeminal nerve.[75]

If no nerve compression is found during surgery, some surgeons perform a retrogasserian rhizotomy by sectioning if nothing is compressing the nerve.[75]

Data in over 5000 patients showed a pain-free rate of between 62–89% after 3–10 years of follow-up. The annual risk of recurrence is < 2% five years post-operative and less than 1% after 10 years. The Outcome was less optimal in TN patients with concomitant continuous pain. In this population, pain freedom rates were 23.5–51% at follow-up after 5 years. MVD is more effective in Classical than Idiopathic TN.[75]

The rates of success of MVD in TN secondary to multiple sclerosis is conflicting. Responder rates are between 39% and 100% with follow-up periods of 12–65 months. It is suggested that a MVD not be done if there is a brainstem lesion related to the TN on MRI. This would be a negative prognostic factor.[76]

MVD is also known as the Jannetta procedure. Peter Jannetta did the first in 1965. Jannetta appeared to have built his neurovascular compression theory, carrying forward the ideas of Drs. Dandy and Gardner, prior the the advent of the operating microscope. In 1965 Jannetta came to the conclusion that TN and hemifacial spasm had the same cause as TN. That year, Jannetta did the first microvascular decompression. He had been surprised to see a superior cerebellar artery pulsing upon the trigeminal nerve root. Interestingly, Jannetta faced at times significant push-back, but he persevered and developed the procedure that remains so helpful today.[77]

In the review of long-term outcome of MVD for TN, it was found that they looked at 1185 patients who underwent MVD during a 20 year history for medically intractable TN. 1155 were followed for a year or more after surgery. The median follow-up period was 6.2 years. Mosty postoperative recurrences of TN took place in the first two years post surgery. 30% of the patients had recureences of tic during the study period and 11% underwent second operations for the recurrences.[78]

Ten years post surgery, 70% of parients had excellent final results- they were free of pain without medication for TN. Four percent had occasional pain that did not require long-term medication usage. Ten years after the MVD, the annual rate of recurrence of TN was less than 1%. It is noted that patients who had previously undergone a prior ablative procedure did not lessen their ability to having a good response to MVD. However, the rates of burning facial pain were higher if a trigeminal ganglion lesion had been created with radiofrequency current prior to MVD. Major complications included two deaths shortly after the MVD (0.2%) and one brainsetem infacrtion (0.1%). One percent of patients (16) had ipsilateral hearing loss. It was determined that “microvascular decompression is a safe and effective treatment for trigeminal neuralgia, with a high rate of long-term success.”[78]

Other papers noted similar findings. MVD provided pain relief in 90% of patients, maintained in 68–88% after 5 years and in 61–88% after ten years. MVD can be repeated if recurrence of pain occurs, with good results. The main risks in this study were CSF fluid leak and ipsilateral hearing loss. A significant benefit is that the function of the trigeminal nerve is preserved.[79,80]

Using MRI technology, and typically looking at the trigeminal nerve, one can identify neurovascular compression by a looped vessel at the entry zone of the trigeminal nerve root, with dislocation of the nerve root.[81] This is worth looking at in the original reference noted.

Crucci et al.[82] shows a wonderful series of MRIs showing 3D reconstructive interference in steady state, pictures of bilateral neurovascurlar contact without morhphological changes of the nerve root with neurovascular contact, compatible with the diagnosis of Classical TN. Again, it is worth looking at these MRIs seen in the reference noted.

In Crucci and Finnerup’s excellent article you can also see a reconstruction of a patient with trigeminal nerve atrophy in a patient with TN as well as indentation and dislocation of the trigeminal nerve root in a patient with TN.[82]

Finally, from Lanbru et.al.[49] is a picture Fig. 2 of a microvascular decompression. The legend reads: “MR scan of the trigeminal nerve and intraoperative pictures during microvascular decompression in patient with classical trigeminal neuralgia. (A) Axial MR 0.5 mm volumetric SPACE sequence through the pons showing neurovascular conflict between the right superior cerebellar artery (SCA) and the right trigeminal nerve (V). (B) Intraoperative view of the right cerebellopontine angle, prior to right microvascular decompression, showing conflict between the right SCA and V. (C) Black and white rendition of the previous photograph with labelling of the superior cerebellar artery, V, and more superficial seventh and eighth nerve complex (VII/VIII). (D) The superior cerebellar artery has been mobilized and transposed superiorly towards the tentorium. It is held in place with a small piece of Teflon (T). (E) A small drop of fibrin glue (F) has been applied to ensure that the T does not migrate. A small ‘dent’ in the course of the trigeminal nerve can be seen at the site of the previous neurovascular conflict. SPACE, sampling perfection with application optimized contrasts using different flip angle evolution.”

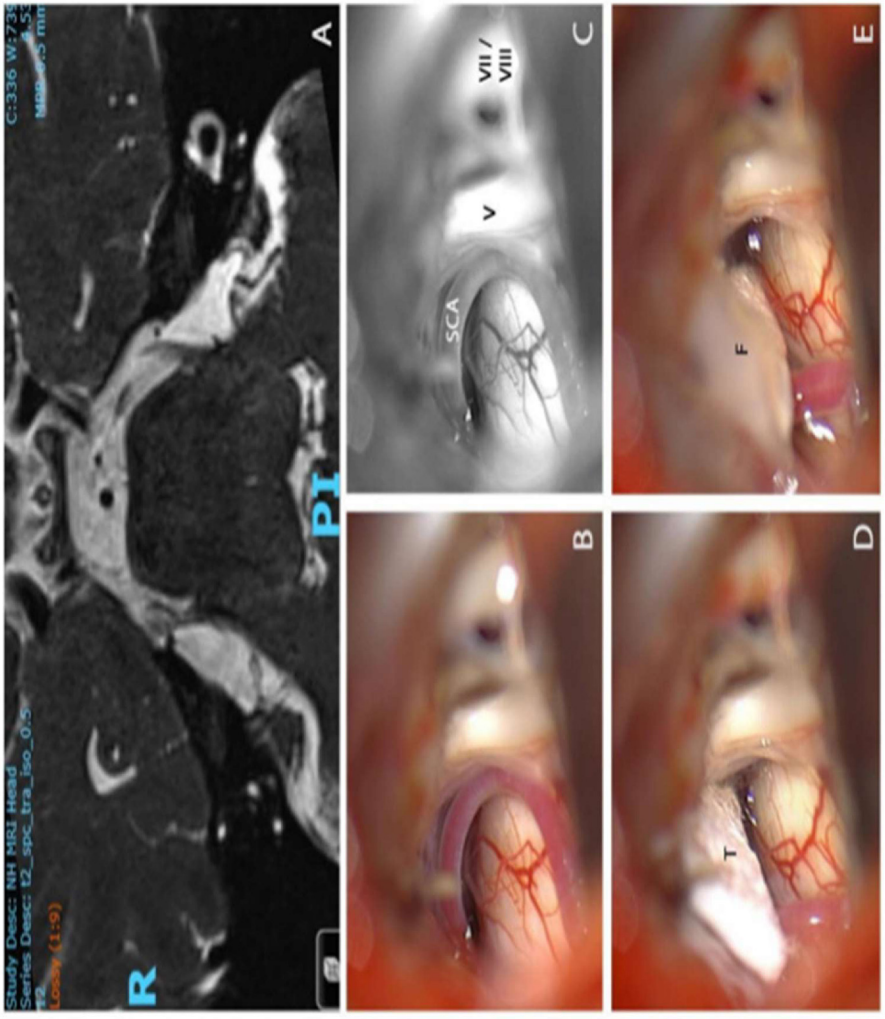


**Fig. 2.** MRI scan of trigeminal nerve (A) and intraoperative pictures (B–E) during microvascular decompression from a patient with TN.

## Stereotactic radiosurgery (SRS)[83–88]

In patients who have failed medical treatment but are not surgical candidates, stereotactic radiosurgery (SRS) can be considered. This would include, via radiation oncology, use of the "gamma knife" or "cyber knife" and other linear accelerator-based modalities. These would include:

- The dorsal nerve root entry zone is targeted, limiting brainstem exposure.
- There is a latency period of 3–6 months to pain improvement with an initial response rate of 70%, which can decrease to 50% at 3 years.
- It is common for patients to continue to need medications after SRS.
- Like a percutaneious rhizotomy, SRS is a destructive procedure that can cause facial numbness.
- Repeat treatment with SRS has been done with lower doses of radiation.
- Complications can include facial paresthesias and V1 numbness, radiation injury to the brainstem and anesthesia dolorosa (painful numbness- very difficult to treat).
  - Classical TN symptoms, response to medications and response to prior procedures predict a favorable response.
  - Postoperative facial numbness has been reported to preduct treatment response.

Several series have reported lower response rates in patients with atypical symptoms or those with secondary TN.

New Strategies include fractionation of the radiation dose and targeting parts of the trigeminal nerve outside of the root entry zone. It is felt that the fractionation may be a good strategy to limit radiation doses to the brainstem. More anterior targeting of the trigeminbal nerve has also been proposed.[89,90]

## Interventional activity: invasive, ablative-controlled lesioning of the trigeminal ganglion or root[91–97]

If there is no evidence of trigeminal neurovascular contact or there are significant comorbidities, ablative procedures can be considered- the least invasive is the previously noted stereotactic radiosurgery (SRS).

New evidence suggests that trigeminal internal neurolysis is effective in the long-term, but has a high complicartion rate (facial hypoaesthesia- 90%).

The percutaneious neuroablative procedures (radiofrequency thermocoagulation, balloon compression, glycerol rhizolysis) all provide on average 3-4 years of pain relief and repetitive ablative procedures are commonly required. The complication rates are high, especially with repetitive procedures. There is no current evidence for one procedure over another.

Percutaneous approaches are ablative procedures that are directed to the Trigeminal Ganglion located in Meckel's Cave.

The goal in treatment is to selectively destroy the A -delta and unmyelinated Cfibers that mediate pain and preserve the A-alpha and beta fibers that mediate touch. Generally, these techniques have an acceptable high rate of initial pain and attack reduction, but the benefit lessnes over time.

The procedures can be repeated.

Significant drawbacks include the potential for the development of anesthesia dolorosa, as well as weakness of facial and masticartory muscles as well as facial anesthesia.

## Proposed treatment algorithm

After the diagnosis of Classical Trigeminal Neuralgia is met, the author would trial first, the sodium channel blockers- carbamazepine (CBZ) or, for the author, more frequently, oxcar-

bazepine (OXC). The latter is easier to titrate and the author has encountered fewer AEs that would make him change to carbamazepine. On the other hand, the author frequenly needs to change from carbamazepine, in patients sent to him on that medication to oxcarbazepine, and titrate upwards. A patient should not be on both sodium channel blocking drugs. Also, it is imperative that electrolyes and CBC be tested for on a repeated basis, as sodium wasting is an AE secondary to OXC, and a reason to stop that medication. Aplastic anemia is a major reason to stop carbamazepine, especially in the elderly patient who may already have an anemia. The author typically won't use CBZ as titration is "stilted" or limited and AEs can be problematic.

Other medications to try if the patient can not tolerate these medications would include lamotrigine or the gabapentinoids (individually or together), as the author has found the side chains in pregabalin do help with gabapentin analgesia if combined.

The author will also use low dose naltrexone in combination with OXC.

If the patient is unable to tolerate the medications or reaches the maximum dosage of approrpate medications and still has severe pain, the patient would be sent to neurosurgery for evaluation for a Trigeminal microvascular decompression (MVD) (an MRI finding of neurovascular compression is part of the initial work-up).

Post MVD, some patients may need some medication if there is not immediate cessation of pain. For these patients, if they haven't been on the sodium channel blockers, they should try them, even Lacosamide and/or low dose naltrexone. Other medications to try may include baclofen, particularly in patients with multiple sclerosis. OnabotulinumtoxinA, if it hasn't been used pre-MVD may be considered if the MVD is not successful. This should be used in a grid, with injections 1 cm apart.

After trying medications, if the patient can not tolerate them or if they are not giving significant pain relief, the use of the more interventional treatments may be considered: SRS- gamma knife surgery, glycerol rhizolysis, radiofrequenty thermocoagulation, balloon compression and internal neurolysis. It is thought that one should not move ahead with internal neurolysis after a MVD.[49]

In the case of Idiopathic TN, The same medications noted above should be tried initially. An MRI should be performed during the workup to rule out a secondary case of TN. Then, if the medications are not satisfactory for any number of reasons, an MVD or interventional treatment may be considered. Microvascular decompression may be utilized in Idiopathic TN first, as AEs are far less than the interventional treatments. Also, neurosurgeons may find neurovascular compression not seen on MRI. For various reasons noted above, MVD would be placed, by the author, before SRS, or other interventional approaches in Idiopathic TN.

Finally, in the case of Secondary TN, in which an underlying cause is found on initial MRI, if the TN continues after treatment of the underlying etiology is completed, one would move ahead with the same medications noted above; this may need to occur earlier than at the end of treatment of a secondary cause of the TN.

Finally, from the author's clinical experience, MVD does not help as much in patients with concomitant, continuous pain. Also, medication management may be more difficult in this population.

An important point brought up by Lambru et.al.[49] is that internal neurolysis should be avoided after a MVD secondary to a higher risk of anethesia dolorosa. Finally, if multiple sclerosis is the secondary cause, don't consider MVD if there is MS with iplilateral pontine plaque.

Finally, remember that in some patients, the TN will wax and wane over time. Some patients may also experience remission periods of varying times, days to months or even years.

## Persistent idiopathic facial pain (PIFP) (atypical facial pain)

Persistent Idiopathic Facial Pain (PIFP) is the term now used for "atypical facial pain". The term was used at least as far back as 2005.[98]

The pain associated with PIFP is dull, poorly localized facial pain of longer duration vs. Classical TN, which is well defined. It is within the distribution of the trigeminal nerve but is not

confined to the distribution of a particular trigeminal division. It is further defined by its duration of > 2 h/day and 3 months or longer duration, with no other definitive cause.[99,101]

The diagnostic criteria of PIFP, per the International Classification of Orofacial Pain (ICOP) is:[100]

(A) Facial pain fulfilling criteria B and C
(B) Recurring daily for > 2 h/day for > 3 months
(C) Pain has both of the following characteristics:
  (1) Poorly localized, and not following the distribution of a peripheral nerve
  (2) Dull, aching or nagging quality
(D) Clinical and radiographic examinations are normal, and local causes have been excluded
(E) Not better accounted for by another ICOP or ICHD-3 diagnosis

The only differences in the International classification of Headache Disorders, 3rd Edition[1], is the inclusion of two statements: The Clinical neurological examination is normal and a dental cause has been excluded by appropriate diagnoses. Also, the pain has no physical signs or sensory loss, and the imaging studies (and blood tests) are negative.

## Epidemiology

The estimated lifetime prevalence of PIFP is about 0.03%, with an indicence rate of 4.4/100,000 person years.[102–104]

In orofacial pain clinics, PIFP[105] may be up to 10–21% of the patient population. In a neurogical tertiary care center for headache and facial pain, about 21–27% had persistent idiopathic facial pain.[106,107]

Only 3% had side-locked unilateral headache and facial pain presenting to the neurology outpatient clinic and were diagnosed with PIFP. Most of these patients were female with a mean age in the mid 40 s.[107]

## Symptomatology

PIFP, at onset, is frequently associated with minor surgical or other invasive dental or ENT procedures reported as the initiating event or done as an attempt to manage the pain. However, most patients can not recall the sequence of events.[108–110]

By definition, these patients have no neurological abnormalities, but they did find hypoesthesia reported in studies using quantitative sensory testing (QST). Patients with a neuropathic type of pain post-operatively or other trauma with neurosensory changes should be diagnosed as painful traumatic trigeminal neuropathy (PTTN), as defined by the IHS.[1,111,112]

Pain described in PIFP is most commonly deep but can be superficial as well; it is poorly localized, radiating and mostly unilateral, but up to 40% have described bilateral pain. PIFP has also been described as aching, burning, throbbing and not infrequently, stabbing. The severity is mild to severe (7/10) and may be increased by emotional stress.[112,113]

Patients with PIFP who complain of severe pain frequently demonstrate a disparity between their apparent calm emotional and physical state and the reported pain severity. Most PIFP patients who report long lasting, persistent daily pain (years) note it tends to spread in a non-dermatomal pattern over time. Also over time, pain characteristics, location and other associated features change. Rarely, some patients diagnosed with PIFP report pain free or remission periods. PIFP may also co-exist with other chronic orofacial pain or headache syndromes.[113–115]

Psychosocial and psychiatric disability have frequenrtly been associared with PIFP. These patients may have increased scores for anxiety and depression, and they frequently report higher pain intensity- for these reasons, a psychiatric screening should be done.[116]

In patients with PIFP or burning mouth syndrome, systemic screening found that 41.3% of patients had an axis 1 disorder, most frequently major depression, prior to the onset of orofacial pain. As one researcher stated, "psychiatric morbidity and cormorbidity to other chronic pain conditions, in chronic idiopathic orofacial pain can best be understood in terms of shared vulnerability to both chronic pain and specific psychiatric disorders".[115,116]

It was felt that an interdisciplinary treatment approach to both diagnosis and management/treatment of PIFP is needed.[117]

## Pathophysiology

Studies have shown that there is no evidence for neurovascular compression of the trigeminal dorsal root entry zone in PIFP. The large number of PIFP patients who present with a history of mild trauma with subclinical sensory changes has led to the thought that PIFP and PTTN may represent extremes of a spectrum of clinical presentation.[102]

That would make PIFP a neuropathic pain syndrome. Studies, in support of this, have found increased neuronal excitability at the brainstem level, distrurbed inhibitory function of the prefrontal cortex and changes in the dopamine systems associated with either pain transmission and modulation, or both.[118–120]

Sensory changes consistent with a neuropathy or neuropathic pain have been found when quantitative sensory testing (QST) was performed in patients with PIFP. These data appear to indicate that PIFP is a neuropathic pain syndrome.[112]

Forssell et.al.[112] indicated the need for a detailed neurophysioloigic and quantitative sensory examination in patients with TN and possible PIFP. That group was the first to think that PIFP may represent one end of a spectrum of pain problems that ranges from definitive neuropathic pain syndromes to idiopathic pain with an unclear "neuropathic" involvement.

Another group found no changes in somatotopy of the somatosensory cortex (via magnetoencephalography) and noted inconsistent changes to the blink reflex in a group if PIFP patients, which indicated no significant changes were found in the trigeminbal somatosensory pathways. PIFP may therefore not always be a neuropathic pain syndrome. In these same patients, QST testing revealed that other than thresholds for warm and heat pain, there was no significant difference in the PIFP group from controls, which would enable possible subtypes of PIFP, neuropathic and other.[113]

It may be appropriate to consider Complex Regional Pain Syndrome (CRPS), which can begin insidiously, by a minor bump of an extremity against a wall that was mild in the extreme (CRPS-Type 1), which used to be called Reflex Sympathetic Dystrophy (RSD), not CRPS Type 2, or causalgia.[121,122]

While CRPS is a chronic, painful neuropathic disorder that develops as a disproportionate consequence to minor injury, it is associated with significant autonomic trophic and motor changes in the extremities, not in the trigeminal regions.[122,123]

Clinically, PIFP may be very difficult to distinguish from a chronic myofascial pain syndrome or chronic tension-type headache with no pericranial muscle tenderness. Could some forms of PIFP be an atypical type of Chronic Tension-type headache with no pericranial muscle tenderness and share pathophysiological elements? Is PIFP, like CRPS, a disproportionate response to a minor injury?[124,125]

The myofascial pain syndrome (MPS) is a collection of symptoms and signs that can occur secondary to the presence of trigger points (TrPs) in skeletal muscle. A TrP is a small focus of exquisite tenderness in muscle that when stimulated by pressure, or irritated, can refer pain to distant sites on the body. The TrP is considered to be the result of an acute or chronic muscle overload that results in contraction of segmental sarcomeres and then the production of nociceptive neurotransmitters and cytokines. TrPs can cause a primary disorder, such as a cervical myofascial pain syndrome, or be comorbidities associated with other conditions such as migraine or more commonly, tension-type headache.[126–129]

In the MPS, pain can be referred to the face. The known referral pain patterns of myofascial trigger points in the neck and face musculature may strongly suggest that at least a subset of PFIP is caused by myofascial trigger points. These localizations were first documented in the trigger point "Bible" written by Janet Travel, MD and Dave Simons, MD.[130]

For example, pain referred from the sternocleidomastoid muscle resembles pain secondary to the pain of PIFP, but other muscles also refer pain to the face.[131]

Trigger points in the upper trapezius and medical pterygoid and anterior and middle temporalis muscles can refer pain to the region of the third division of the trigeminal nerve (V3). TrPs in thbe deep masseter muscle refer pain to the region of V2 and V3. TrPs in the sternaocleidomastoid muscle refers pain to V1 and V2. TrPs in several head and neck muscles can induce facial pain localized to one or more divisions of the trigeminal nerve secondary to referred pain from the TrPs.[131–133]

As noted above, referred pain patterns of TrPs in neck and head muscles may refer pain to the face in various trigeminal nerve distributions. Below is an example- the names of the muscles which have a referred pain pattern are shown. Note that the sternocleidomastoid muscle can refer to the side of the face primarily in the distribjution of V2 as well as more commonly, referral over the eye (V1). Bruxism and tooth clenching may activate muscles associated with the temporomandibular joint and may be activated in disorders of the joint.[132]

One can also view these referred pain patterns in 24 different views in this article Fig. 3 which depicts figures designated as 3 to 8 represented in the reference 126 article in Disease A Month. Figs. 4–10

While PIFP is rare, syndromes that are PIFP-like may be associated with significant underlying pathology.

There are other chronic facial pain syndrome that must be considered to rule out PIFP.

The first would be trigeminal neuralgia, with shock-like, lancinating pain. See above for more on TN.

Postherpetic neuralgia- (shingles) has pain which persists more than 3 months after the initial rash is healed. The pain is neuropathic, and has allodynia and hyperalgesia. It most commonly effects V1, the opthalmic distribution of the trigeminal nerve. Treatment may include AEDs, TCAs and SSRIs.[134]

Temporomandibular Joint (TMJ) syndrome- symptoms may include: tenderness or pain in the jaw; pain in one or both TMJs; problems or pain when chewing; aching pain in and around the ear; aching facial pain. The quality of the pain is similar to that of PIFP- that is dull, aching even burning. Treatment of TMJ syndrome may be directed at the articular joint itself, or at the temporalis muscle or the periodontal ligament.[135,136]

Cluster Headache (acute and chronic)- sudden onset of severe pain in one eye and/or temple, which is burning, boring, quite severe in nature, lasting 30 to 180 min at a time. A patient will become agitated to the point of self injury. The pain may occur multiple times a day. Ipsilateral autonomic signs include tearing, conjunctival injection and rhinorrhea. It may be treated with a triptan, oxygen has been used, but is not well reimbursed. Verapamil is a major drug treatment, with lithium carbonate and/or valproic acid.[137]

Migraine Headache- can be bilateral but mostly unilateral. About 18% of women and 6% of men in the USA have migraine.The pain is throbbing and is typically associated with nausea, possibly vomiting, phtophobia, phonophobia and osmophobia. The pain will worsen with exertion. About 20% of migraine patients have migraine with typical aura (visual, sensory, or speech/cognitive). Treatment is either prophylactic or abortive. There are four older preventatives (beta blockers, calcium channel blockers, AEDs), or the newer drugs, the CGRP humanized antibodies. The typical abortives are triptans, which are vasoconstrictors; the newer CGRP gepants (small molecules) are not.[137]

The Cluster-Tic syndrome is very interesting- it has three types of pain. It can be like trigeminal neuralgia; it may have, in another form, cluster headache like features, or, in the third type, a combination of both types of pain- neuralgic pain immediately followed by homolateral headache with autonomic signs, the type of pain that is more pathogenic for this entity. It can be episodic or chronic and treatment is poor, but may include AEDs,TCAs ad SSRIs or NSRIs.[138]

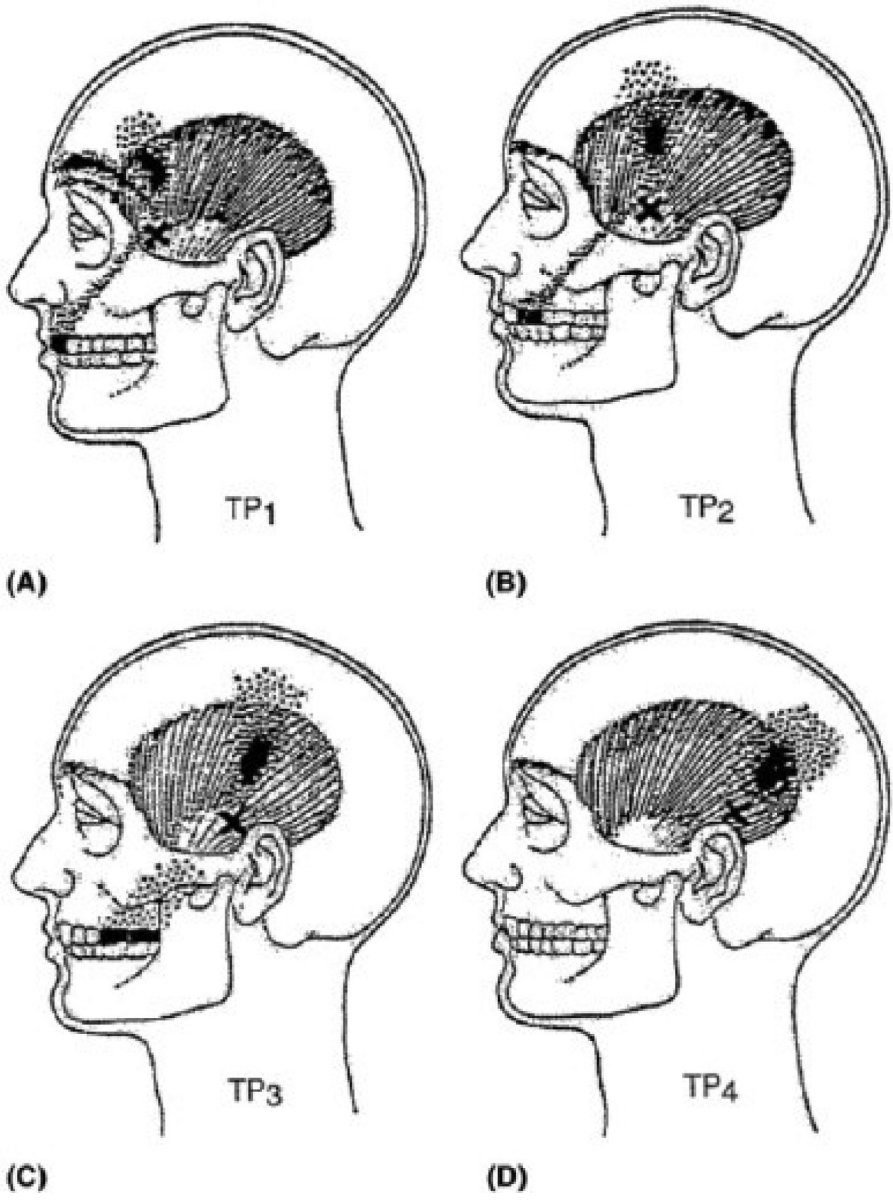


**Fig. 3.** Referred pain patterns from trigger points (X) in the left temporalis muscle. Dark areas show essential zones; spillover zones are stippled. (A) Anterior "spokes" of pain arising from the anterior fibers- trigger point 2 region (B and C) Middle Spokes- trigger pint 2 and 3 regions. (D) Posterior supra-auricular spoke- trigger point 4 region.[126]

Primary stabbing headache (icepick headache)- Sharp stabbing pain typically in various trigeminal nerve divisions can be seen. It may also occur in other divisions. Subclassifications include monophasic, intermittent and chronic forms. The clinician may want to perform neuroimaging. Indomethacine remains the primary treatment, with other options including COX2 inhibitors and melatonin.[139]

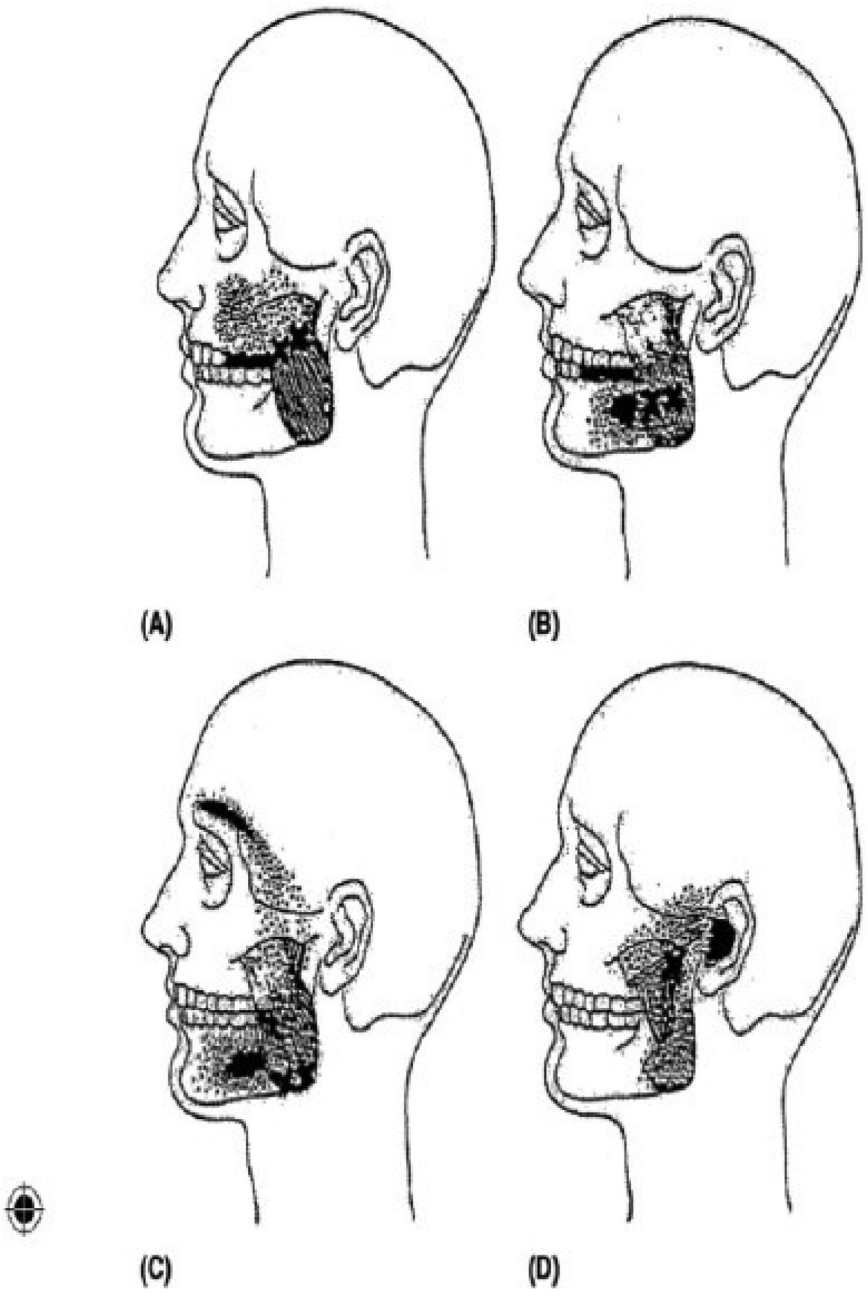


**Fig. 4.** Each X indicates a trigger point in various parts of the masseter muscle. Dark areas show essential zones; spillover zones are stippled. (A) Superficial layer, upper portion. (B) Superficial layer, mid-belly. (C) Superficial layer, lower portion. (D) Deep layer, upper part, just below the temporo mandibular joint.[126]

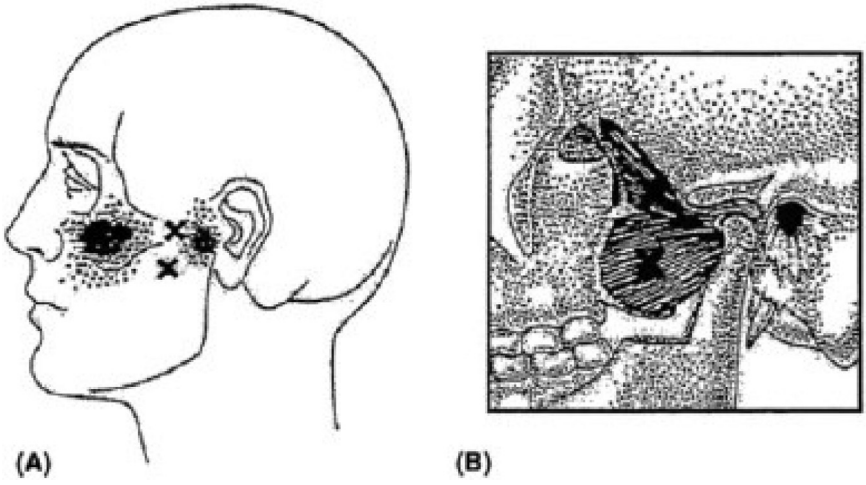


**Fig. 5.** Referred pain pattern (A) of trigger points (X) in the left lateral psterygoid muscle (B).[126]

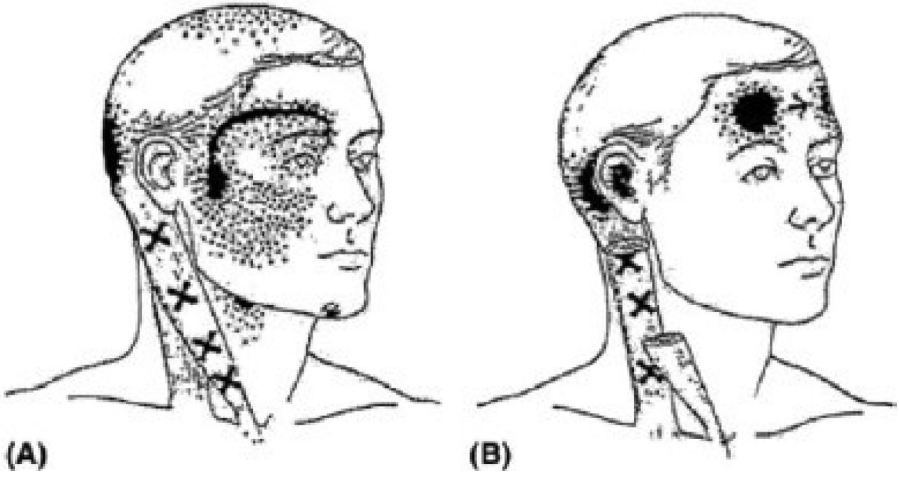


**Fig. 6.** Referred pain patterns with location of corresponding trigger points (X) in the right sternocleidomastoid muscle. In B, note the effects in the ear. This may be associated with vertigo. Dark areas show essential zones; spillover.zones are stippled. (A) The sternal (superficial) division; (B) the clavicular (deep) division.[126]

SUNCT, or Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing, and SUNA (Short- lasting unilateral neuralgiform headache attacks) may, per published studies, have demonstrated that demographics and clinical phenotypes of SUNCT and SUNA have a significant overlap with TN.[45] All-together, this evidence suggested that SUNCT and SUNA and TN may constitute a continuum of the same disorder.[48] Lamictal is the treatment of choice at this time.[137]

Hemicrania Continua, another Trigeminal Autonomic Cephalalgia, is characterized by unilater headache and facial pain. The head pain is continuous, with pain exacerbations that may occur with variable frequency (multiple times a day, week or even every second or third month). Baseline pain is moderate or even mild, with the exacerbations being moderate to severe in pain intensity. It may be associated with migraine or cluster headache as it has some similar

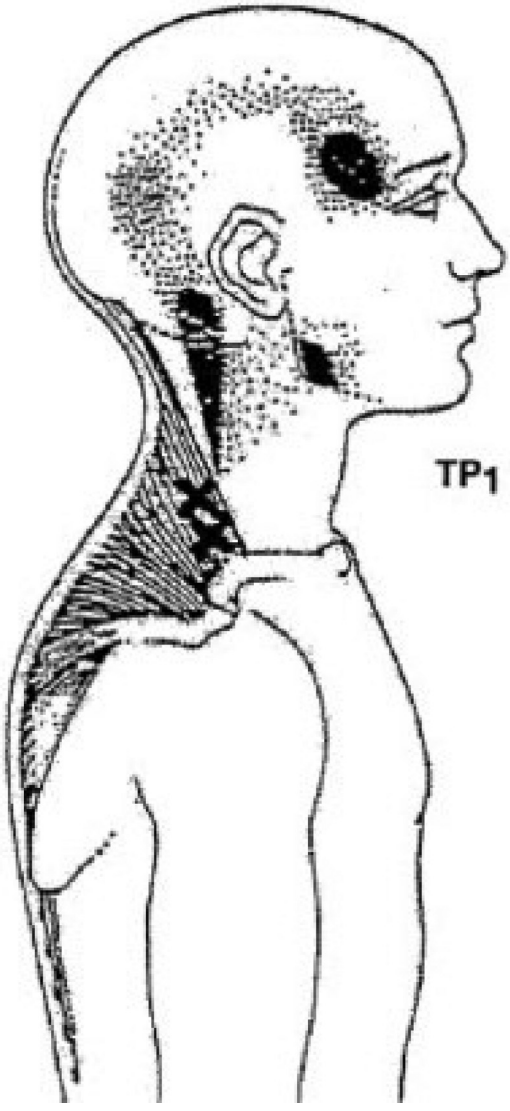


**Fig. 7.** Referred pain pattern and location of trigger point (X) in the upper trapezius muscle. Dark areas show essential zones; spillover zones are stippled.[126]

features (photophobia, nausea, aura, lacrimation and scleral injection). Hemicrania Continua responds well to indomethacin, and this also verifies the diagnosis.

Raeder Syndrome (or the Raeder paratrigeminal syndrome (RPS), or paratrigeminal neuralgia, is an uncommon neurological disorder characterized by unilateral oculosympathetic paralysis (i.e., Horner syndrome) which now seems to mean any painful postganglionic Horner's syndrome. However, there is a V1 distribution of ipsilateral burning facial pain associred with hyperesthesia, ptosis and miosis. Sweating is maintained. The clinician must rule out a middle cranial fossa lesion, syphilis or sinusitis; trauma may initiate the problem. The pain may be self-limited in the absence of a secondary source of etiology.Treatment depends on etiology and in some cases may be secondary to disease of the carotid artery.[136,140,141]

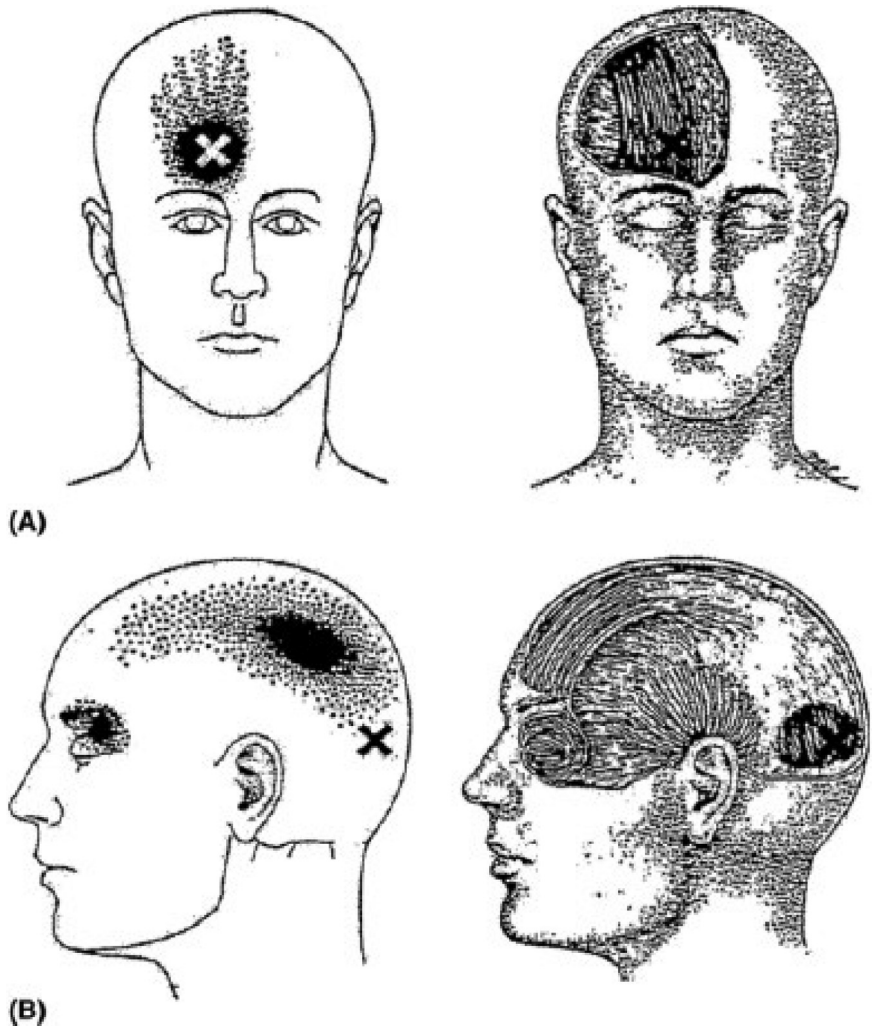


**Fig. 8.** Pain patterns (shaded areas) referred from trigger points (X) in the occipitofrontalis muscle, commonly associated with unilateral, supraorbital, or ocular headache. (A) Right frontalis belly; (B) left occipitalis belly[126]

The Thalamic Pain Syndrome is secondary to a lesion of the ventral-medial thalamic nuclei. It consists of unitlateral burning facial pain and dysesthesias. The pain is severe, burning or aching, localized to the contralateral face. The diagnosis can be made by imaging studies, as well as the presence of other associated symptoms in thr limbs or trunk. It is a form of central post-stroke pain with spontaneous pain and attacks of allodynia and hyperalgesia. Studies have shown limited evidence for the use of amitriptyline, opioids, anticonvulsants, transcranial magnetic stimulation, and acupuncture in the treatment of central post-stroke pain. Deep brain stimulation is a possible treatment option for refractory cases. Radiation therapy is another viable treatment option for refractory cases of central post-stroke pain. First-line therapy for central post-stroke pain includes desensitization of the tactile stimulus, causing pain. Amitriptyline has been the most widely studied drug in the treatment of central post-stroke pain. Furthermore, trazodone and venlafaxine are also considerations. Some studies suggest lamotrigine may be the most effective anticonvulsant in the treatment of central post-stroke pain. Amitriptyline

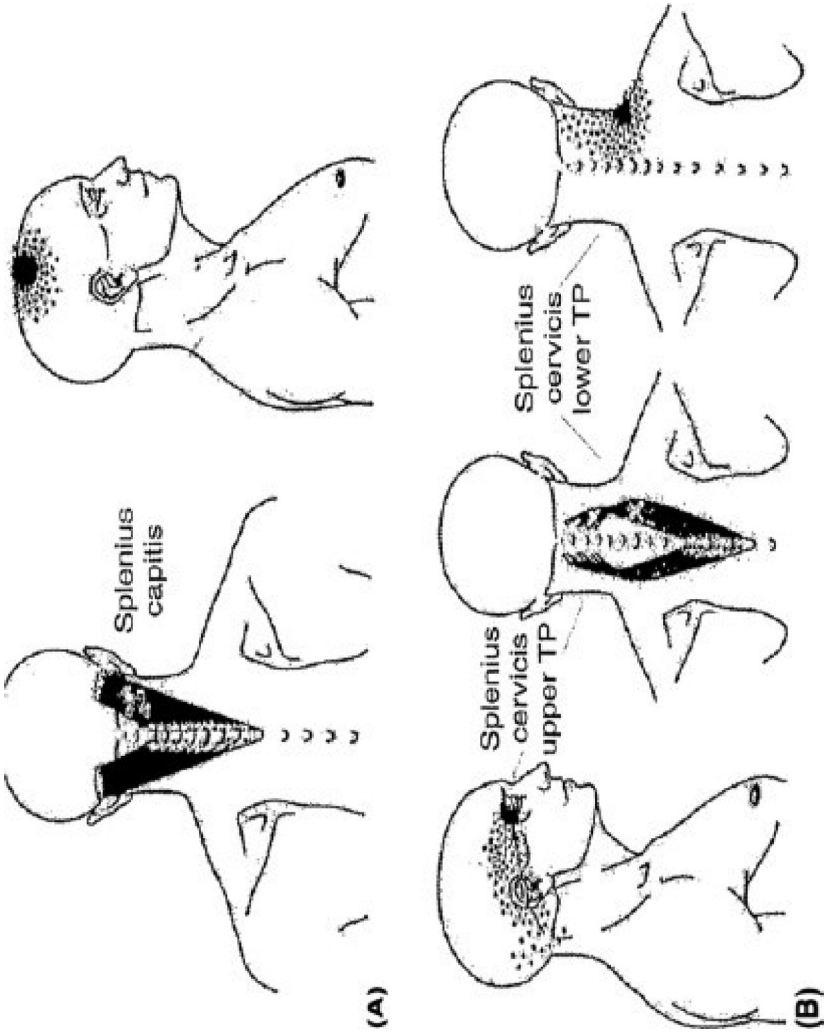


**Fig. 9.** Trigger points (X) and referred pain patterns (shaded areas) for the right splenius capitis and splenius cervicis muscles. (A) Splenius capitis trigger point that overlics the occipital triangle; (B) left, the upper splenius cervicis trigger point (TP) refers pain to the orbit. The dashed arrow represents pain shooting from the inside of the head to the back or pain shooting from the inside of the head to the back of the eye. Right, another site of pain referral.[126]

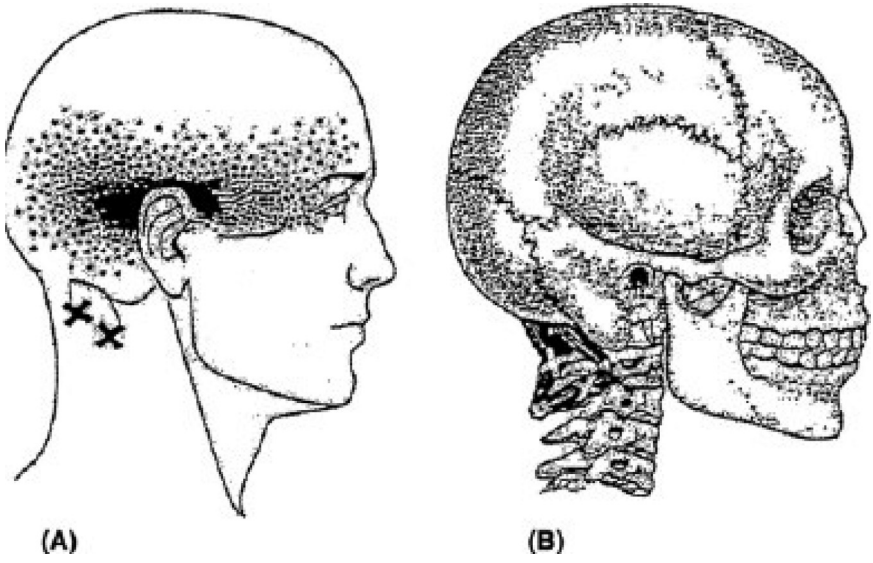


**Fig. 10.** (A) Referred pain pattern (shaded area) (A) of trigger points (X) in the right suboccipital muscles (B).[126]

has been found to be more effective in patients with spinal cord injury and comorbid depression. Not surprisingly, there have been mixed results in multiple studies regarding the efficacy of pregabalin and gabapentin in central post-stroke-related pain and central pain related to spinal cord injuries.[142–147]

Taking all those into account, this would leave the typical differential diagnosis, including some of these etiologies:[136]

Brainstem Gliomas
Cluster Headache
Migraine Headache
Migraine Variants (don't forget the 3 aspects of a "Typical Aura")
Migraine in Children
Temporomandibular Dysfunction
Trigeminal neuralgia
Chronic paroxysmal hemicrania
SUNCT/SUNA

Obtaining a cerebral MRI or CT scan can be important to rule out other diagnostic considerations:[136,148,149]

Brainstem syndromes
Dymyelinating disease, peripheral or central
Malignant and non-malignant pain syndromes
Temporomandibuilar disorder

## Painful traumatic trigeminal neuropathies (PTTN)

Another issue that must be considered are the painful traumatic trigeminal neuropathies (PTTN).

Generally, injuries to the trigeminal nerve typically result in either no residual neurological deficit or a non-painful neuropathy.

Three to five pervcent may develop a painful neuropathy and it is felt that sex, previous pain experiences, deficiencies in pain modulation and genetics are involved. Many of these patients develop pain after dental/endodontal procedures: specifically, some of the issues follow root canals, persistent post-endodontic pain, nerve injuries after dental injection and trigeminal nerve injury post-third molar surgery.[150–162]

Macrotruama (Secondary to fights and Motor Vehicle Accidents) are major initiating factors to PTTN. Iatrogenic injuries from facial, otolanyngological or neurosurgical, dental procedures (extractions, root canals, implants)- all procedures that may pose a risk of neuropathy secondary to direct or indirect neuronal trauma. Injury from dental nerve blocks has been implicated in PTTN. The pain would be unilateral and be precisely located to the dermatome of the affected nerve with demonstrable sensory dysfunction.[150–162]

Over time, PTTN may “escape” a dermatome and become more diffuse and spread across multiple dermatomes. The pain intensity if moderate to severe (5–8/10), with a burning or shoot quality to the pain typical of neuropathic pain.[163]

In some cases, patients may report excruciating pain which is both spreading and distant, which increases with light touch, a triggering-like mechanism, but these are rare. There is no latency or refractory period as in trigeminal neuralgia. More often, there is clinically severe allodynia, hyperalgesia or negative neurosensory signs which would be typically absent in PIFP. Hyperalgesia and other sensory changes may be found in extratrigeminal sites of PTTN patients, suggesting that more extensive changes in central somatosensory processing occurs. The pain is continuous, lasts most of the day, on most days, and there may be a feeling of swelling, a foreign body or hot or cold and even local redness.[159–165]

PIFP is associated with changes in intracortical modulation which involves GABAergic mechanisms, possibly relating this to the pathogenesis of PIFP.[166]

Kawasaki et al looked at two groups of patients, those with or without neurovascular compression (NVC) of the trigeminal nerve. They found that the group without NVC had significant headache, noncardiac chest pain, shortness of breath and pain catastrophizing. They concluded that PIFP patients can be divided into two groups- one with a neuropathic pain phenotype when NVC was present and the second having a functional somatic symptom phenotype, presenting without NVC.[167]

Agostoni et al note that PIFP is really a diagnosis of exclusion.[168]

Weiss et. al. noted that PIFP is an excruciating disorder of the face which is often misdiagnosed as trigeminal neuralgia. They do note that unlike TN symptoms, the pain of PIFP is persistent rather than intermittent, typically unilateral and without autonomic signs or symptoms. They concluded that when a patient with neuropathic facial pain is encountered, and the symptoms are do not lead to the diagnosis of a common etiology, the diagnosis of PIFP must be “entertained”. They do note that PIFP should be treated in a multidisciplinary treatment program. Finally, they note that there are few randomized controlled trails for treatment of PIFP.[169]

PIFP rarely occurs in children. Sakurai et al reported on an 11 year old boy who initially presented with right cheek pain and a streptococcal infection. When seen and facial cellulitis was suspected, this was resolved with antibiotic treatment. The right cheek pain recurred within 4 weeks. As the antibiotic treatment did not relieve the boy’s pain, he was seen at an outpatient clinic. Physical examination revealed facial tenderness in the V2 region, which suggested TN. An MRI was performed and there was no neurovascular compression. The continuous dull and nagging aspevts of the pain differed from TN, with its sudden, severe pain. PFIP was then diagnosed. The boy had prolonged nausea, listlessness, headache and anorexia and pain. Psychological councelling found stress related to his life out of school. He was taught stress management and he improved. It was thought that this case demonstraited the psychogenic aspects of PIFP and the value of psychlogical counseling.[170]

## Facial pain

Migraine and the Trigeminal Autonomic Cephalalgias are classically located around the ocular and frontal regions. Cases have been reported of isolated oral and facial pain with neurovascular features which suggest facial or orofacial migraine. The isolated "facial migraine" is very rare (0.2%). These atypical presentations have caused misdiagnoses with dental and maxillary sinus pathology.[171–175]

Ziegeler and May[176] looked at 2,912 patient datasets. Two hundred ninety one patients reported facial pain associated with primary headache. In patients with migraine, 2.3% (44 of 1,935) reported a facial involvement, typically in V2. Of this patient set, 18 patients (40.9% reported pain mostly in the face. In cluster headache patients, 14.8% (42 of 283) had facial involvement, with 31% reported the pain as predominately in the face. Facial involvement was was also seen in patients with various TACs, including paroxysmal hemicrania, hemicrania continua and patients with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headaches attacks with cranial autonic symptoms (SUNA).

They concluded that facial involvement in primary headache was infrequent but not uncommon. They also found six patients with constant side-locked facial pain with superseded well-defined facial pain attacks lasting 10 to 30 min, occurring several times a day. They felt these patients might represent a new entity that they suggested could possiblty be called "constant unilateral facial pain with added attacks".[176]

In their paper, Ziegeler and May[176] demonstrated an excellent representation of their patient sample (2,912) with headache and facial pain in Fig. 11 (4).

## Misdiagnosed PIFP

The misdiagnosis of PIFP can occur if the clinician does not recognize atypical or rare orofacial pain syndromes such as atypical neurovascular pain, regional myofascial pain and especially other neuropathic pain syndromes.[177]

PIFP may also be part of a spectrum of neuropathic mechansms on one end, and painful traumatic trigeminal neuropathy on the other. Patients with atypical neurovascular pain, regional myofascial pain and atypical regional neuropathic pain may be misdiagnosed as having dental or otolaryngologic or otolaryngical pathology. Invasive procedures may be done and then you have patients with the diagnosis of PIFP and/or painful traumatic trigeminal neuropathy. Either diagnosis may be used, as part of a spectrum, and the etiology may be missed or interfered with via a surgery that may or may not be necessary.[177]

## Clinical issues

### *Examination*

It is the author's experience and belief that these patients are best evaluated and worked up via an interdisciplinary approach to diagnosis and treatment.

Clinical neurological examination of these patients is most typically negative. The general examination regarding PIFP is also negative.

Part of the examination should be for musculoskeletal myofascial issues. If approrpiate you may consider a dental examination. A psychiatric evaluation can also be an important aspect of the evaluation. Psychological testing, typically done by a psychologist, can also be important.

Because of some of the aspects of the differential diagnosis, an MRI of the brain, with and without contrast, may be very helpful.

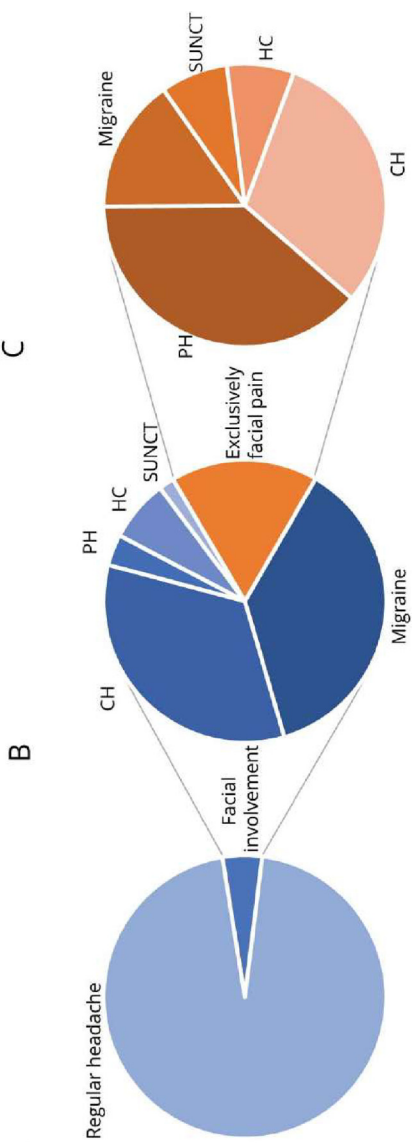


**Fig. 11.** Distribution of facial representations in a sample of 2,912 patients headache and facial pain. 176
All patients with primary headache with the percentage of patients with headache with a facial involvement. (B) The separate entities of primary headache disorders with a facial involvement. (C) Pain syndromes exclusively affecting the face. CH = cluster headache; HC = hemicrania continua; PH = paroxysmal hemicrania; SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

## Treatment

Unlike the treatment of other facial pain syndromes such as trigeminal neuralgia, the treatment of persistent idiopathic facial pain (PIFP) is neither as helpful or satisfactory. It is therefore important to understand the way medications work, as it is not as easy as using a sodium channel blocking AED as for Trigmeninal Neuralgia. The clinician must understand that typically a single drug won't do it, and it is the clinician's understanding of how various medications including antidepressant medications (ADMs); or specific drugs such as the tricylic antidepressants (TCAs), the norepinephrine serotonin re-uptake inhibition (NSRIs); the N-methyl-D-aspartate receptors (NMDARs) (for depression and pain); the antiepileptic drugs (AEDs); topical anesthetics; cannabidiol (CBD) receptor agonists tetrahydrocannabinol (THC); substance P delpletion agents and opioid analgesics.

The key here is to understand the use of drugs of various types being used simultaneously in a safe manner, as adverse events will enduce patients to stop the medications, and therefore, provide less possible help. Medication interactions should also be kept high up in your mind.

## Medications

*Antiepileptic medications (AEDs) anticonvulsants (ACDs)*

*Carbamazepine*

A sodium channel blocker and first line medication for the treatment of trigeminal neuralgia. The FDA-approved medical uses are epilepsy (including partial seizures, generalized tonic-clonic seizures and mixed seizures), trigeminal neuralgia, and manic and mixed episodes of bipolar I disorder. The FDA-approved medical uses are epilepsy (including partial seizures, generalized tonic-clonic seizures and mixed seizures), trigeminal neuralgia, and manic and mixed episodes of bipolar I disorder. It preferentially binds to voltage-gated sodium channels, preventing sustained and repetive firing of action potentials. There is evidence that carbamazepine is a serotonin releasing agent. It is possibly a serotonin reuptake inhibitor. Other literature notes that the medication may depress the activity of the thalamic nucleus ventralis. It may also decrease synaptic transmission or the summation of temporal stimulation, which would lead to neural discharge as it limits the influx of sodium across the cell membrane or via other currently unknown mechanisms of actions. Aplastic anemia is a known AE. Typical dosing is 200 mg TID to 400 mg TID maximum[136,178–182]

*Oxcarbamazepine*

Oxcarbazepine (OXC) may be substituted for carbamazepine (CBZ) and is a useful alternative to carbamazepine in patients with trigeminal neuralgia.[183,186] OXC may be better tolerated than carbamazepine. OXC may be better tolerated than Carbamazepine, but has the potential for a serious side effect- hyponatremia.[183,187]

The mechanism of action involves the blockade of sodium currents but differs from CBZ by modulating different types of calcium channels. While CBZ is oxidized by the cytochronic P-450 system, OXC goes through reductive metabolism to form a monohydroxy derivative which is glucuronidated and excreted in the urine. When switching from CBZ to OCX, it does normalize CBZ associated thyroid and sexual hormone abnormalities. OXC also appears to be better tolerated than CBZ; it causes fewer rashes than CBZ.[184] CBZ undergoes autoinduction and reaches steady state in 3 to 5 weeks at a stable dose. CYP450 3A4 metabolism produces an active epoxide metabolite. While OXC is very useful in the management of TN, studies have not shown it to be useful for other forms of neuropathic pain, such as diabetic peripheral neuropathy.[185]

Dosages for TN may range from 150-450 mg TID, with a maximum dosage of 2400 mg/day.

*Gabapentinoids*

Gabapentin; Pregabalin

The data for Gabapentin for the treatment of PIFP is a bit sketchy, but not as bad as the data for the treatment of TN, with 16 Chinese articles without good experimental design.[188] It is felt that this calcium channel drug with efficacy at the alpha-2-delta subunit of voltage-gated calcium channels, which reduces excitatory neurotransmitters, like Pregabalin, may be helpful after the use of the sodium channel blockers. These medications may be considered second line, if not alternative treatments.[189] As noted above, FIPF is considered by many to be neuropathic in nature.

Gabapentin is related structurally to gamma-aminobutyric acid (GABA) but it does not interact with the GABA receptors. The oral bioavailability of gabapentin is approximately 80% at 100 mg administered three times daily once every 8 h, but decreases to 60% at 300 mg, 47% at 400 mg, 34% at 800 mg, 33% at 1,200 mg, and 27% at 1,600 mg, all with the same dosing schedule and continues to get lower as the dosages increase. The oral bioavailability of pregabalin is greater than or equal to 90% across and beyond its entire clinical dose range (75–900 mg/day) it can, but not typically treat trigeminal neuralgia.[190]

The best evidence exists for gabapentin treatment of postherpetic neuralgia and diabetic neuropathy. It does not treat trigeminal neuralgia.[191,192]

In terms of number needed to treat, gabapentin shows moderate effectiveness for neuropathic pain. Only a minority of patients obtain meaningful relief. Out of 10 persons treated with gabapentin, three to four benefit substantially as compared to one to two persons treated with placebo.[192]

Pregabalin has been approved for use in postherpetic neuralgia and painful diabetic peripheral neuropathy, as well as for Fibromyalgia. It is given equal weight as gabapentin and tricyclic antidepressants as a first line agent for some neuropathic pain syndromes (diabetic neuropathy, post-herpetic neuralgia and central neuropathic pain), however the latter drugs tend to be less expensive.[179,193,194]

Particularly with Pregablin, renal issues, with a decrease in creatinine clearance can cause decreased elimination and thus higher plasma concentrations.[190] As with patients with Fibromyalgia and headache, it may be necessary to treat the Fibromyalgia first which may make treating the headache, or facial pain (PIFP) easier.

Pregabalin may induce significant issues of sexual dysfunction including erectile dysfunction, anorgasmia and loss of libido. These were not dose related.[195]

The London Pain Clinic notes that in treating atypical facial pain, Gabapentin and Pregabalin are two of 4 medications they would use, the others being capsaicin and amitriptyline.[196]

*Lamotrigine*

Lamotrigine is used for seizures and psychiatric issues. Lamotrigine is a sodium channel blocking AED, which may suppress the release of glutamate and aspartate, both excitatory neurotransmitters. The drug is unique, having little in common with other sodium channel blocking AEDs[197,198]

While in 2008, a study found that Lamotrigine was effective in treating a number of pain and neuropathic pain syndromes including central neuropathic pain, trigeminal neuralgia, trigeminal neuralgia in multiple sclerosis, pain in multiple sclerosis, SUNCT, cluster headache, glossopharyngeal neuralgia, neuropathic pain, allodynia, neuralgia after nerve resection, postherpetic neuralgia, and HIV associated neuropathic.[199]

Around the same time, Eisenberg et al reviewed 5 open trials and 6 or seven randomized controlled trails and reported that the efficacy of lamotrigine in the treatment of various forms of neuropathic pain was positive.[200]

In 2013 Wiffen, Derry and Moore[201] in a Cochrane Database Systematic revue, concluded that lamotrigine's lack of efficacy in chronic pain did not change. They stated that studies "provided no convincing evidence that lamotrigine is effective in treating neuropathic pain and fibromyalgia at doses of about 200 to 400 mg daily."

Several more recent studies showed that lamotrigine alone or in combination with pregabalin, did show evidence of efficacy in the treatment of central post-stroke neuropathic pain. The side effects of lamotrigine were not insignificant.[202,203]

*Topiramate*

Topiramate, a carbonic anhydrase inhibitor, which only rarely can cause clinically important metabolic acidosis.[204]

This medication is used to treat epilepsy, migraine, and idiopathic intracranial hypertension.[204]

There are a number of mechanisms of action, as the cellular targets include: volage gated sodium channels; high-voltage-activated calcium channels; AMPA/Kianate receptors; GABA-A receptors and carbonic anhydrase isoenzymes.[205]

Topiramate has not been shown to work as a pain treatment for in diabetic neuropathy, the only neuropathic condition in which it has been adequately tested with multiple trials (4 RCTs with 1684 people).[206]

A number of significant AEs exist, including teratogenicity.[207] Topiramate can cause acute myopia and secondary angle closure glaucoma in a small subset of people who take topiramate regularly which can lead to permanent visual loss. These symptoms, which typically appear in the first month of treatment, include blurred vision and eye pain. The clinician should question the patient regarding any opthalmological events during office visits. Discontinuation of topiramate may halt the progression of the ocular damage and may reverse the visual impairment.[208]

Topiramate can also cause renal stones- avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis or in patients on a ketogenic diet.[208] These renal calculi are calcium phosphate stones, not calcium oxalate. An increase in hydration is beneficial to the patient.

There is one patient case report showing that topiramate stopped persistent idiopathic facial pain in a patient with what looked like, but was not hemicrania continua. It was first used with imipramine, which was tapered off and the patient did well on just the topiramate.[209] Topiramate decreases efficacy of oral contaceptives by CYP3A4 induction. Physical barrier methods should be considered. Topiramate can cause weight loss in costrast to gabapentinoids weight gain and peripheral edema.

*Phenytoin*

This medication may stabilize the neuronal membranes and treat neuralgia by increasing efflux or decreasing influx of sodium ions across cell membranes of the motor cortex, all during the generation of nerve impulses. It should be noted that the half-life is dependent on the concentration, so steady-state serum levels may take as long as 3 weeks to develop.[136]

Phenytoin is one of the medications that be used for the treatment of atypical facial pain.[221]

## Antidepressants (ADs)

*Tricyclics (TCAs)*

*Amitriptyline and nortriptyline*

The TCAs, generally inhibit reuptake of serotonin and norepinephtine at the synapses. The tertiary amines are more serotonergic and the secondary amines are more noradrenergic. Amitriptyline, a tertiary amine, is the most anticholinergic of the TCAs, with the most sedation, xerostomia, and other anticholinergic effects. Nortriptyline, a secondary amine is the least anticholinergic of the drug class and is the secondary amine metabolite of amitriptyline.

This medication has been used for the treatment of Headache (Tension-type and Migraine with/without typical Aura). This medication was also the first used to treat fibrositis, what we now call Fibromyalgia secondary to Harvey Moldovsky's work in the 1970s. In 1975, Modofsky, Scarisbrick P, England R, Smythe H, deprived college students of stage 4 sleep and found that they developed a sleep disorder, alpha intrusion into state 4 sleep (alpha-delta sleep disorder) as well as musculoskeletal symptoms.[211]

Other studies replicated this: one study found abnormal brain metabolism of substances including serotonin, which is implicated in sleep arousal as well as pain mechansms, were ameliorated by the use of tricyclic antidepresants and SSRIs, both of which were felt to be useful in the treatment of fibromyalgia. It was also noted that aside from the alpha-delta sleep disturbance, these fibromyalgia patients may have also have had, along with the non-restorative sleep disorder (the alpha-delta abnormality), sleep apnea or period leg movements. The alpha-delta EEG sleep anomaly was not specific to fibromyalgia.[212,213]

It has been shown that amitriptyline and other TCAs suppress REM sleep but significant as well as sustainedly.[214,215]

Nortriptyline also changed the EEG in a pattern similar to amitriptyline, with REM latency and REM sleep time decreased by the TCA usage.[216]

Inspite of these issues, use of amitriptyline to treat PIFP is very common. Guler et al.[217] noted that data from their study of long-term follow-up of patients with atypical facial pain treated with amitriptyline did well on the medication and felt it may be preferred in patients with atypical facial pain. Other groups found that the most used medications to treat PIFP and PTTN were amitriptyline and clonazepam. Figuerola et al.[218] found that judicious polypharmacy may be needed for some patients. Ziegeler et al, in their review article "Idiopathic Facial Pain Syndromes"[219] -noted that patients with continuous facial pain (PIFP, PTTP) were best treated with tricyclics or anticonvulsants.

An earlier study found that amitriptyline was effective in the treatment of patients with a somatoform pain disorder of the orofacial region.[220]

*NSRIs (SNRIs)*

These medications, also called non-tricyclic serotonin and norepinephrine reuptake inhibitors, are second generation antidepressants after TCAs. The SNRIs, including venlafaxine, milnacipran and duloxetine, can produce a more balanced inhibition of serotonin and norepinephrine reuptate inhibition. While milnacipran inhibits both serotoneric and noradrenergic reuptake, it has a preference for norepinephrine reuptake inhibition and it also has an association with the NMDA receptors.[222]

Venlafaxine receptor affinity is dose dependent. It acts as more a serotonin reuptake inhibitor at low dosage, and with increasing drug dosages, a norepinephrine reuptake blocker effect is noted.[223] Desvenlafaxine, the active metabolite of venlafaxine has been approved by the FDA for major depressive disorder.[224]

Presynaptic SNRIs reuptake inhibition of norepinephrine increases the levels of norepinephrine which couples not only with postsynaptic alpha- and beta-adrenergic receptors, but also with the presynaptic alpha-2 receptors. These presynaptic receptors have a significant role in antinociception in the CNS. Spinal administration of alpha-2 agonists produces significant analgesia in both animals and humans.[225,226,227]

While there are no postsynaptic effects, venlafaxine has been shown to block sodium channels. This is not similar to the tricyclic antidepressants which are potent volgate-gated sodium channel blockers, even with local anesthetic type effects.[228–230]

Much data exists showing the usefulness of antidepressants (SNRIs) inducing inhibition of serotonin and norepinephrine reuptake leading to enhanced spinal cord descending inhibition of centrally sensitized pain. It does appear that medications with the most prominent effects on

antinociception are inhibitory neurotransmitters whose actions are primarily on the descending antinociceptive or inhibitory pain pathways.[231,232]

The cortex begins the descending input, continuing to the hypothalamus, amygdala and the pretectal nucleus, which then procedes to the midbrain periaqueductal gray, the rostroventral medulla and the dorsolateral pontomesecephalic tegmentum, which projects to the spinal dorsal horn. This descending pathway forms the pain-modulating circuitry which, like most aspects of the CNS, consists of both facilitatatory and inhibitory aspects.[232–234]

With that background, it should come as no surprise that duloxetine shows excellent pain reduction in patients with chronic non-organic pain in the orofacial region.[235,236]

Duloxetine has also been found to decrease pain from diabetic peripheral neuropathy.[237]

Duloxetine has been approved to treat major depressive disorder (MDD), generalized anxiety disorder (GAD), fibromyalgia, diabetic neuropathy, chronic musculoskeletal pain, including chronic osteoarthritis pain and chronic low back pain.[238] Hepatic enzymes should be checked routinely with use of this medication.

Venlafaxine was found to be only minimally effective in the treatment of PIFP.[239.]

Milnacipran is approved to treat major depressive disorder and fibromyalgia. However, two studies show its effectiveness for PIFP. The first, by Ito et al.[240] showed that treatment with milnacipran caused a significant improvement of chronic orofacaisl pain, regardless of concurrent depression. A second study by Kimura et al.[241] showed that the analgesic effect of milnacipran was decreased when the drug was outside of its therapeuric range: treatment of depression was not.

### *Topical Medications*

#### *Lidocaine*

This was the first patch approved for post-herpetic neuralgia in 1999. This 5% lidocaine patch has been used off label for low back pain, fascial pain aside from post-herpetic neuralgia and muscle pain/spasm.[242,243]

#### *Capsaicin*

The use of a Capsaicin 8% patch has been successful at depleting substance P from peripheral sensory neurons. Typically, patients must be prepared with lidocaine gel for an hour prior to this treatment.[244]

#### *Alternative treatments*

First, the author must note that the most effective treatment for a PIFP patient is interdisciplinary, with psychiatric evaluation and treatment of major import.

Other possible treatments: occipital nerve blocks do not effect PIFP.[245,246]

A small study has been done with a low-level energy diode laser.[247]

Accupuncture and neuromuscular enhanced muscle re-education have also been used.[248,249]

## Some final thoughts on treatment

Again, it would be best if treatment of PIFP is performed using a bio-psycho-social or interdisciplinary treatment protocol.

You need to consider the presence or absence of significant psychiatric comorbidities.

Unfortunately, not all therapeutic trials of PIFP have been randomized or controlled. There have been various series done with TCAs, an open trial with duloxetine, a randomized trial with

venlafaxine and a number of open studies using various anticonvulsants. In the bulk of this paper the author has tried to use the best trails, RCTs if at all possible.

Treatment may engender:

(1) Tricyclic Antidepressants (Amitriptyline)
(2) Serotonin norepinepthrine reuptake inhibitors (SNRIs)- including duloxetine
(3) Antiepileptics (lamotrigine, gabapentinoids, oxcarbazepine)
(4) Low dose naltrexone
(5) Trigger point injections for active trigger points in a myofascial pain syndrome
(6) Cognitive behavioral therapy

Other aspects of treatment may encompass:

Ultra-high frequency transcranial electrical stimulation; low level laser, considerations of a sphenopalatine ganglion block, cannabinoids at a patient's discretion (high number of rebound headaches, but patients request to use CBD), and finally, if there is a possibility of a temporomandibular joint dysfunction, and/or gnathic dysfunction, patients will be sent for appropriate evaluations by specialists in those areas.

The author has used the treatments labeled 1-6 frequently for his PIFP patients. He will typically start with one medication such as an ACM or ADM, depending on the patient, and add on a second medication. Psychological evaluation is important.

Psychiatric evaluation and treatment- especially Cognitive Behavioral Therapy is most helpful.

An Interdisciplinary treatment approach is most helpful- the author did that for 26 years.

The Bottom-Line: PIFP is rare, and PIFP-like syndromes may be associated with significant pathology.

A multidisciplinary or an interdisciplinary approach to diagnosis and treatment is essential.

At the very least, a clinician must have a group of experts that can perform PIFP specific evaluations on patients and share the results, even over the phone with the clinicians who have evaluated the patient.'

Sometimes, what may appear simple, is anything but simple- and it is up to the clinician to determine the elements, all the elements, that may be at play; engaging the patients' expectations and treatment limitations is an important step in this journey.

Requisite to initiating pharmacotherapeutic management is a thorough knowledge of the specific essentials to judicious prescribing. This knowledge base includes current information applied to the intended pharmacotherapy which includes but is not limited to the following areas: pharmacology, pharmacokinetics, pharmacodynamics, cautions, black box warnings, contraindications, laboratory and clinical monitoring, parameters, adverse effects, doses with renal and or hepatic dysfunction, pulmonary and cardiac function, drug interactions, food interactions, geriatric/pediatric cautions, safey issues, pregnancy and breast feeding cautions, social and recreational drugs, nicotine,cannabis and alcohol use history. Describing the CYP 450 interactions is provided for the pharmacotherapy discussed in this article (See Table 2). Remaining current with the information prescribed is highly recommended. A key to prescribing is the prescriber education, training, experience, judgement and wisdom focused on whom to prescribe medications and for whom not to prescribe medications while evaluating any risks versus any perceived benefits.

**Table 2**
CYP 450 events of the pharmacotherapy discussed.

| Pharmacotherapy | Substrate | Inhibition | Induction |
|---|---|---|---|
| carbamazepine | 2C8,3A4 | | 1A2,3A4,2B6,2C9 |
| oxcarbazepine | 3A4 | | 3A4 |
| lamotragine | | | |
| gabapentin | | | |
| pregabalin | | | |
| botulinum toxin type A | | | |
| baclofen | | | |
| eslicarbazepine | | 2C19 | 3A4 |
| lacosamide | 2C19, 3A4,2C9 | | |
| vixotrigine | | | |
| onabotulinum toxin A | | | |
| amitriptyline | 1A2,2C9,2C19,2D6,3A4 | | |
| naltrexone (compounded) | | | |
| fosphenytoin | 2C19, 3A4,2C9 | | 3A4,1A2,2B6 |
| lidocaine all forms | 1A2,2A6,2B6,2C9,3A4 | | 1A2,3A4 |
| verapamil | 1A2,2B6,2C9,2E1,3A4 | | |
| lithium | | | |
| valproate | 2A6,2B6,2C9,2C19,2E1 | | |
| CGRP humanized antibody | | | |
| "gepants" | | | |
| atogepant | 3A4 | | |
| remegepant | 2C9,3A4 | | |
| urogepant | 3A4 | | |
| venlafaxine | 2C9,2C19,2D6,3A4 | 2D6 | |
| trazodone | 2D6,3A4 | | |
| tetrahydrocannabinol(THC) | 2C9,3A4 | | 1A2 |
| cannaabidiol(CBD) | 2C19,3A4 | 1A2,2D6,2C19,3A4,5,7 | |
| capsaicin | | | |
| topiramate | | 2C19 | 3A4 |
| phenytoin | 2C9,2C19,3A4 | | 1A2,286,3A4 |
| nortriptyline | 1A2,2C19,2D6,3A4 | | |
| milnacipran | | | |
| duloxetine | 1A2,2D5 | 2D6 | |
| desvenlafaxine | 3A4 | | |
| cannabinol | 2C9,3A4 | | |

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