

Comprehensive Review

Neurostimulation for the Treatment of Chronic Head and Facial Pain: A Literature Review

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Conflict of interest: Dr. Antony is a consultant for Abbott, is on the product advisory board for Boston Scientific, and has sponsored research (PI) with Abbott/Nevro. Dr. Hunter is a consultant and researcher for Abbott, Saluda, and Nuvectra, and was previously a consultant for Nevro. Dr. Mazzola and Dr. Dhaliwal do not have any conflicts of interest to report. None of the authors of the manuscript received any remuneration. Further, the authors have not received any reimbursement or honorarium in any other manner for the work on this manuscript.

Manuscript received: 12-19-2018
Accepted for publication:
03-29-2019

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Background: Head and facial pain is a common and often difficult to treat disorder. Routine treatments sometimes fail to provide acceptable relief, leaving the patient searching for something else, including narcotics and surgery. Recently, neuromodulation has been expanding to provide another option. Secondary to its potentially temporary nature and relatively manageable risk profile, several reviews have suggested trialing neuromodulation prior to starting narcotics or invasive permanent surgeries. There is evidence that neuromodulation can make a difference in those patients with intractable severe craniofacial pain.

Objectives: To provide a basic overview of the anatomy, epidemiology, pathophysiology and common treatments of several common head and facial disorders. Furthermore, to demonstrate the suggested mechanisms of neuromodulation and the evidence currently existing for the use of neuromodulation.

Methods: A comprehensive review was performed regarding the available literature through targeting articles reporting on the use of neuromodulation to treat pain of the head and face.

Results: We compiled and discuss the current evidence available in treating head and facial pain. The strongest evidence currently for neuromodulation is for occipital nerve stimulation for migraine, transcutaneous vagal nerve stimulation for migraine and cluster headache, sphenopalatine ganglion microstimulation for cluster headache, and transcutaneous supraorbital and supratrochlear nerve stimulation for migraine. In addition, there is moderate evidence for occipital nerve stimulation in treating occipital neuralgia.

Limitations: Neuromodulation has been trialed and is promising in several craniofacial pain disorders; however, there remains a need for large-scale, randomized, placebo-controlled clinical trials to further evaluate the efficacy and safety of most treatments. Much of the current data relies on case reports without randomization or placebo controls.

Conclusions: With advancing techniques and technology, neuromodulation can be promising in treating intractable pain of the head and face. Although more randomized controlled trials are warranted, the current literature supports the use of neuromodulation in intractable craniofacial pain.

Key words: Neuromodulation, headache, facial pain, craniofacial pain, migraine, cluster headache, trigeminal neuralgia, occipital neuralgia, peripheral nerve stimulator, high cervical spinal cord stimulator, peripheral nerve field stimulator

Pain Physician 2019; 22:447-477

Neuromodulation is an ever-expanding field that has been used for the treatment of chronic pain disorders for the last 50 years. Although the predominant use of neurostimulation has been for the treatment of conditions such as failed back surgery syndrome, complex regional pain syndrome and the like, it has expanded over time to include pelvic pain (1), traumatic neuropathies, diabetic neuropathies, and postherpetic neuralgia (PHN) (2). Recent developments in waveform technology have brought promising potential advancements to the field (3). In addition to targeting dorsal column fibers via leads placed in the epidural space, tonic stimulation of both peripheral nerves and subcutaneous unnamed small fibers of peripheral nerves has been employed for pain control (2). As the understanding, technology, and proven efficacy of peripheral neurostimulation has improved, newer extracranial and intracranial modalities have shown promise in treating headache and facial pain. There is growing consensus among the pain community that extracranial and intracranial modalities be considered prior to starting chronic, long-term opioid therapies in certain conditions refractory to conservative medical management (4).

FACIAL ANATOMY/INNERVATION

Headaches and facial pain can be difficult to diagnose and treat often because of the confluence of complex anatomic structures and sensory systems. The trigeminal cranial nerve (CN V) and its ophthalmic (CN V1), maxillary (CN V2), and mandibular (CN V3) divisions provide sensory innervation to the face via their cutaneous terminal branches. These branches relay sensory input and converge at the Gasserian ganglion (also known as trigeminal or semilunar ganglion) located in Meckel's cave (5). Cutaneous branches of each such as the supraorbital, infraorbital, and mental nerves can be targeted for various therapeutic interventions (4).

Trigeminal Nerve

The trigeminal nerve carries much of the general sensory information from the head, and also innervates the muscles that move the lower jaw. At the level of the middle cranial fossa, the sensory root forms the trigeminal ganglion that holds the cell bodies of these sensory neurons. Of note, the motor root lies below and separates proximal to this point. From the Gasserian ganglion arise the aforementioned 3 divisions of sensory nerves: the ophthalmic nerve, the maxillary nerve, and the mandibular nerve (6).

Ophthalmic Nerve

The ophthalmic division enters the orbit through the superior orbital fissure. It carries sensation from the cephalic part of the anterior face covering the skin from the nose, upper eyelids, upper bridge of nose, scalp, and forehead, as well as sensation from the cornea, mucosa of nasal cavity, and frontal paranasal sinuses. This nerve has various divisions (6).

The supraorbital and the supratrochlear nerves leave the orbit superiorly and are responsible for transmitting sensation from the eyelid, forehead, and scalp. The supraorbital nerve passes through the frontalis muscle and continues superiorly providing coverage over the anterior scalp to the vertex of the head. Similarly, the supratrochlear nerve passes through the frontalis and continues across the anterior forehead supplying the center of the forehead (7). Both these peripheral nerves have been targeted for pain relief as they are easily accessible at a location of maximal nociception where they superficially traverse under the subcutaneous tissue at the forehead (8).

Maxillary Nerve

The maxillary nerve exits the cranial cavity through the foramen rotundum and enters the pterygopalatine fossa. It supplies the skin including the upper lip, lower eyelid, upper teeth and gums, mucosa of the nose, maxillary and ethmoid sinuses, and palate (7).

The infraorbital nerve is a peripheral branch that exits the maxilla through the infraorbital foramen and provides sensation to the lower eyelid, cheek, side of the nose, and upper lip. Similarly, the zygomaticotemporal branch exits the zygomatic bone to supply sensation over the anterior temple located above the zygomatic arch (7).

Mandibular Nerve

The mandibular nerve passes through the foramen ovale as it emerges from the cranium. Of note, the motor component of the trigeminal nerve also exits through the foramen ovale, where it unites with the sensory division. This nerve transmits sensation from the skin over the mandible including the lower lip and side of head. In addition, it supplies the lower teeth and gums, temporomandibular joint (TMJ), mucosa of mouth, and anterior two-thirds of the tongue (6).

The auriculotemporal nerve, a collateral branch off of the posterior division of the mandibular nerve, enters the face just behind the TMJ. The nerve runs laterally to the mandible neck, passing anterior to the

ear and continues cephalically to innervate the ear, the external auditory conduct, the external side of the tympanic membrane, and the temporal region. Furthermore, it innervates the TMJ and carries parasympathetic fibers to the parotid gland (7).

Facial Nerve

The facial nerve (CN VII) carries multiple nerve fibers. The nerve leaves the cranial cavity through the internal acoustic meatus and forms the geniculate ganglion. The general sensation is transmitted from the external acoustic meatus and deeper parts of the auricle. Taste sensation is provided from the anterior two-thirds of the tongue. Parasympathetic autonomic regulation is provided to the lacrimal gland, submandibular and sublingual salivary glands, and glands in the mucous membranes of the nasal cavity and palates. It is at the location of the geniculate ganglion where the facial nerve gives off the greater petrosal nerve that carries the majority of the parasympathetic fibers. The origin of the greater petrosal nerve is the sphenopalatine ganglion (SPG). Furthermore, the facial nerve innervates the muscles for facial expression (7).

Glossopharyngeal Nerve

Glossopharyngeal nerve (CN IX) is a cranial nerve with both sensory and motor components and exits through the jugular foramen. Glossopharyngeal general sensory cell bodies are located at the superior ganglion. The visceral sensory and special cell bodies are located at the inferior ganglion and these synapse at the nuclei of solitary tract. Somatic sensory portion has its cell bodies located in the superior ganglion and synapse at the nucleus of trigeminal nerve. The glossopharyngeal nerve is responsible for general sensation from the external ear, posterior third of tongue, tympanic membrane, isthmus of fauces, and pharyngotympanic tube (6). Furthermore, it receives taste sensation from the posterior third of the tongue, chemoreceptor inputs from the carotid body, baroreceptor inputs from the carotid sinuses, and provides parasympathetic innervation to the parotid gland (7).

The glossopharyngeal nerve travels between the internal carotid artery and the internal jugular vein, located deep to the styloid process and the muscles that attach there. It curves around the border of the stylopharyngeus muscle where it continues anteriorly to reach the base of the tongue. The stylohyoid muscle attaches superiorly to the styloid process of the temporal

bone and inferiorly to the body of the hyoid bone. It contracts to elevate and retract the hyoid bone in effect elongating the floor of the mouth (7).

The Vagus Nerve

The vagus nerve (CN X) also exits through the jugular foramen. The cell bodies are contained inside or just outside the jugular foramen in the inferior and superior ganglions. The vagus nerve transmits visceral sensation from the base of tongue, pharynx, larynx, trachea, bronchi, heart, esophagus, stomach, and intestines (6). Additionally, it transmits general sensation from the auricle, external acoustic meatus, and dura mater of the posterior cranial fossa. It leaves the head and neck to deliver parasympathetic fibers to the thoracic and abdominal viscera (7). Because of this broad coverage, many studies have targeted this nerve to treat a multitude of diseases.

Sphenopalatine Ganglion

The SPG lies in the pterygopalatine fossa and receives sensory, parasympathetic, and sympathetic input. The pterygopalatine fossa lies immediately posterior to the upper jaw or the maxilla and is the location where the maxillary nerve emerges from the cranial cavity. The parasympathetic root comes from the greater petrosal nerve from the facial nerve and the nucleus of origin is the superior salivatory nucleus. The sympathetic system follows the deep petrosal nerve that is a branch of the internal carotid plexus that is a continuation of postsynaptic fibers from the cervical sympathetic trunk. The fibers from superior cervical ganglion pass through the SPG and enter branches of maxillary nerve (6). The SPG has connections to the facial nerve, lesser occipital nerve (LON), and the cutaneous cervical nerves (9). It is stimulated by trigeminal afferents and affects cerebral vascular tone and blood flow. It is a key structure responsible for cranial and facial autonomic symptoms in conditions such as trigeminal neuralgia (TN) and cluster headache (CH) (10).

Otic Ganglion

The otic ganglion, inferior to the foramen ovale, lies between tensor veli palatini and mandibular nerve. The parasympathetic innervation comes from the tympanic nerve from the glossopharyngeal nerve. The sympathetics are from fibers of the superior cervical ganglion that travel via a plexus on the middle meningeal artery (6).

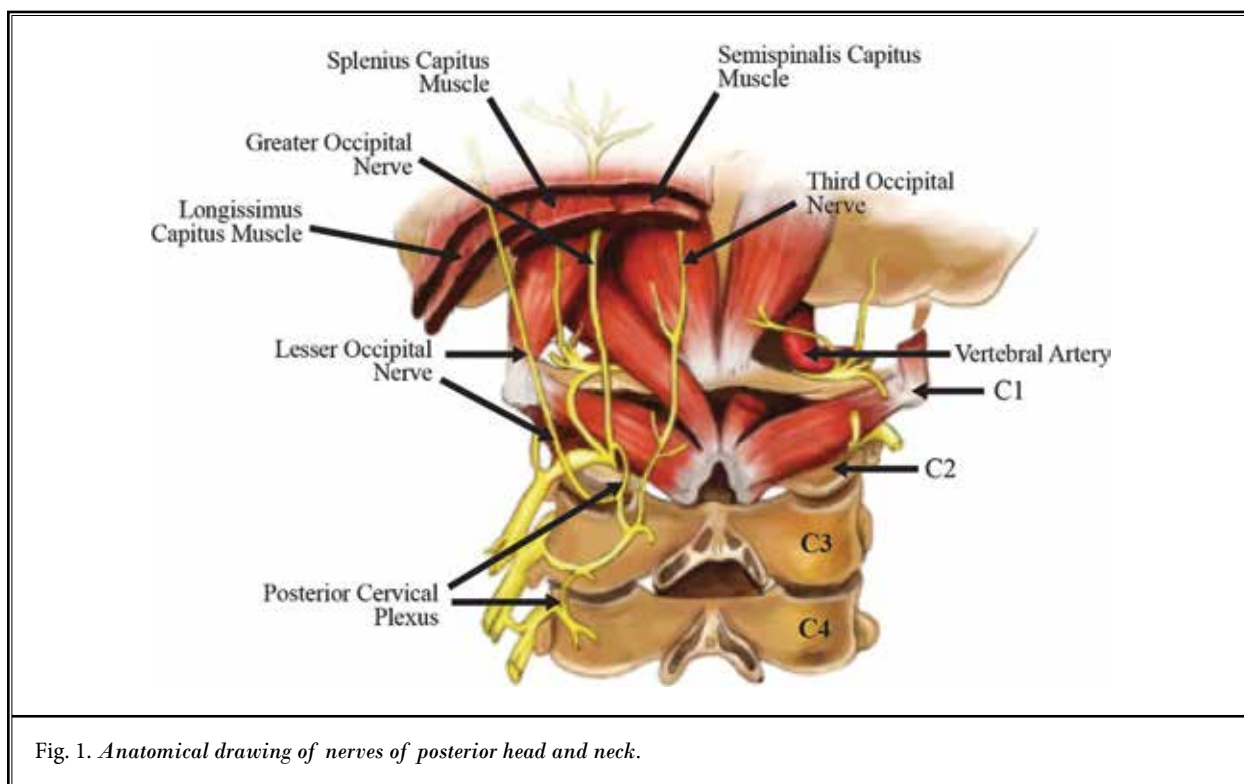


Fig. 1. *Anatomical drawing of nerves of posterior head and neck.*

Great Auricular Nerve

The great auricular nerve is a branch of the cervical plexus (Fig. 1). It arises from the anterior rami of C2 and C3 spinal nerves, and superiorly follows the sternocleidomastoid muscle where it provides sensory innervation to a small area of the scalp behind the ear (7).

Lesser Occipital Nerve

The LON, another branch of the cervical plexus, arises from the lateral branch of C2 (sometimes C3) and provides sensation to a more inferior portion of the occiput (11). It provides innervation to an area posterior and superior to the ear (7).

Greater Occipital Nerve

The greater occipital nerve (GON) branches from the posterior ramus of the C2 spinal nerve where it emerges under the obliquus capitis inferior muscle, moves cephalically to the suboccipital triangle until it pierces the semispinalis capitis and the trapezius muscle. Here it spreads out to supply a large portion of the posterior scalp up to the vertex (7).

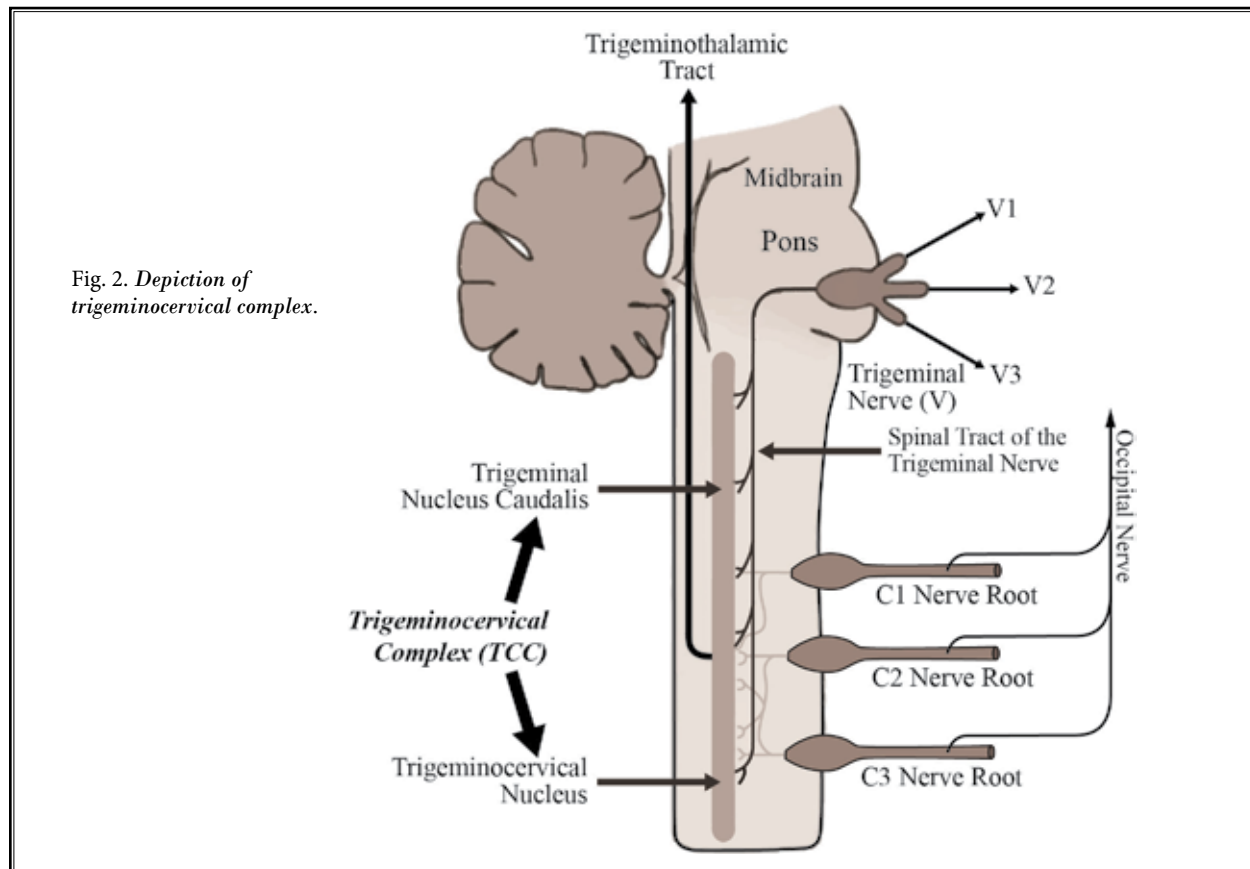
Third Occipital Nerve

The third occipital nerve is a branch of the poste-

rior ramus of the C3 spinal nerve. It emerges through the semispinalis capitis and the trapezius muscle where it supplies a small portion of the lower scalp in the suboccipital region and the zygapophyseal joint C2-C3 (7).

Trigemincervical Pain Pathway

This trigeminal system provides the infrastructure for pain and touch sensation to the face and the motor function of the muscles of mastication. The system goes from the midbrain and medulla, including the mesencephalic nucleus, the main sensory nucleus, a spinal nucleus of CN V, and the motor nucleus. The spinal nucleus of the trigeminal nerve includes the subnucleus oralis, the subnucleus interpolaris, and the subnucleus caudalis. This subnucleus caudalis acts as the dorsal horn and reaches as far caudally to the second (C2) or third cervical level (C3). It is in the nucleus caudalis that the primary afferent synapses and where the second order neuron crosses to form the contralateral spinothalamic tract. It is postulated that activation of nuclei near the trigemincervical complex may explain the symptoms of aura and other associations common with certain types of headaches (12). Several studies have demonstrated this network connection (Fig. 2) and describe a trigemincervical pain pathway where activation of



one part of the system leads to a response in other areas (13). Activation of the superior sagittal sinus has the ability to activate from the trigeminal nucleus caudalis to C1 and C2 of the dorsal horn. Through stimulation of the GON, metabolic activity increases in the dorsal horn at C1 and C2, and the trigeminal nucleus caudalis (14). Matharu et al (15) analyzed positron emission tomography of 8 patients with chronic migraine (CM) who all responded to implanted bilateral suboccipital stimulators. This functional brain imaging demonstrated thalamic activation response to occipital nerve stimulation (ONS). Therefore because of this connectivity, there are additional interconnected sites that may be targeted. The complex anatomic structures involved in facial pain make assessment and diagnosis difficult, but also offer many potential targets for therapeutic intervention.

TYPES OF FACIAL PAIN

Migraine

Migraine headaches are a common disorder that affects 36 million individuals in the United States

alone (16). A study of the global burden of disease in 2015 placed migraine as number 7 of the leading causes of years lived with disability (17). Recently, a one year prevalence of migraines was estimated to be as high as 11.7% to 13.2% in the United States (18). The most affected range from age 25 to 55 years with a predominance of women (19). Classically, migraines are described as pulsating pain to one side of the face lasting from a few hours to a few days that may or may not include nausea, vomiting, changes in vision or hearing. These headaches usually occur above the canthomeatal line in a frontotemporal distribution and last from 4 to 72 hours. Children and adolescents are likely to have bilateral headaches that become unilateral by age 18 years. A small portion of women, < 10%, may have migraines associated with their menstrual cycle. Based on the characteristics of the headache, migraines can be further classified into different subtypes that includes migraine with aura, migraine without aura, abdominal migraine, retinal migraine, episodic migraine, and CM, among others. They can be debilitating, as many who suffer from this condition

require bed rest that detracts from social and occupational function (20).

Prophylactic treatments include beta blockers, tricyclic antidepressants, calcium channel blockers, and anticonvulsants. Triptan drugs and nonsteroidal anti-inflammatory medications remain the most common options for acute symptomatic treatment (17). Approximately 14% of those with episodic migraine treated at a specialized headache center progressed to CM regardless of medication usage. Some studies have suggested that medication overuse can actually predispose one to chronicity (21). Refractory CMs has been shown to respond well to peripheral stimulation of the occipital nerve (22).

Cluster Headache

CH presents as severe unilateral periorbital pain lasting 15 minutes to several hours that is associated with autonomic symptoms of the face, eyes, and nose. Thus it falls under the grouping of trigeminal autonomic cephalalgias. The attacks tend to follow a circadian pattern in which they often occur at the same time of day, and there is a propensity for nocturnal attacks. CH lifetime incidence is believed to be approximately 50 cases per 100,000, with 3 times as many men affected than women. First-degree relatives are 14 to 48 times more likely to have CH than the general population (23). It usually affects individuals between age 20 and 40 years (24). Generally, attacks occur in a group of series that can last for weeks or months separated by months or years of remission, categorized into episodic CHs, in which attacks occur in series lasting from 7 days to 1 year, and chronic CH in which attacks last for 1 year or longer with remission periods < 3 months (20).

Abortive treatment includes oxygen and serotonin antagonists. Verapamil is the first-line prophylactic agent but other medications such as steroids, topiramate, and ergotamine have been employed (25). Overall, 15% to 20% of patients with chronic CH do not effectively respond to pharmacologic monotherapy. Refractory chronic CH has also been shown to respond to supraorbital nerve and SPG stimulation (4).

Occipital Neuralgia

Occipital neuralgia is a condition characterized by sharp, stabbing pain in the occiput that is often accompanied by allodynia and occipital tenderness (26). General population incidence has been suggested to be 3.2 per 100,000 per year. Chronically contracted muscles and spondylosis of the upper cervical spine have been

correlated with irritation of either the GON or LON (27). Common presentation is with shooting, sharp severe pain that recurs lasting from a few seconds to minutes (20). Pain is most commonly unilateral and found in the distribution of the GON. Often idiopathic, other mechanisms such as posttraumatic or even whiplash-induced nerve damage have been proposed.

Medical treatments include anti-inflammatory medications, neuropathic pain medications, and anti-epileptic drugs. Occipital nerve blocks and pulsed radio-frequency (PRF) lesioning of both the greater occipital and LONs have been employed (26). The Neuromodulation Appropriateness Consensus Committee concluded that occipital stimulation for occipital neuralgia was a recommendable treatment modality in conditions refractory to conservative medical modalities (4).

Burning Mouth Syndrome

Burning mouth syndrome (BMS) has been used to describe idiopathic chronic oral mucosal pain. It generally involves burning or itching of the oral mucosa, which is sometimes accompanied by xerostomia and dysgeusia (28). BMS is most frequently reported in perimenopausal or postmenopausal women (12%-18%), although the general population prevalence varies on average from 1.0% to 3.9%, with one review suggesting as low as 0.01% (29). Those affected most commonly range from age 50 to 60 years (30). Patients commonly present with a daily intraoral superficial burning sensation that lasts at least 2 hours per day for > 3 months, without any evidence of lesions or pathology of oral mucosa. Pain often fluctuates in strength and is bilateral with predominance to the tip of the tongue (20). The etiology appears to be multifactorial, and although the pathophysiology is not clearly understood, current literature supports involvement of peripheral and central neuropathic pathways, whereas other theories involve mast cell activation and vitamin B12 deficiencies (31-33).

Currently treatment consists of a multidisciplinary approach consisting of stabilizing underlying medical conditions, supportive therapies, and behavioral feedback (34). These modalities have been largely unsatisfactory. A Cochrane review by McMillan et al (35) analyzed current treatment modalities such as antidepressants and antipsychotics, anticonvulsants, benzodiazepines, cholinergics, dietary supplements, electromagnetic radiation, physical barriers, psychological therapies, and topical treatments. They concluded that there is insufficient evidence to support

or refute the use of any interventions in managing BMS. A review by Rodríguez-de Rivera-Campillo et al (36) concluded that partial improvements could be seen in approximately 60% of patients if one of their treatments included topical clonazepam. However, the majority of patients respond with partial to no relief and often find themselves constantly trialing multiple medications in attempt to alleviate their symptoms. A blind, placebo-controlled randomized trial treated 12 patients suffering from BMS with prefrontal repetitive transcranial magnetic stimulation. Umezaki et al (37) concluded that there was a significant pain reduction after one week of treatment compared with the placebo control group. Seven patients in the treatment group and 5 in the sham reported mild headaches that disappeared after 1 or 2 days. Based on our literature review, there is no evidence to support that peripheral neuromodulation can be an effective treatment modality for patients with BMS.

Trigeminal Neuralgia

TN is a condition that causes unilateral, paroxysmal, facial pain. It is mediated by a branch of the trigeminal nerve. Although rare in the general population, TN incidence progresses with age, affecting 2 to 5 per 100,000 per year in the general population and increasing up to 25 per 100,000 per year in people aged > 70 years (38). Women are 1.5 to 1.75 times more likely to be affected. Trigeminal neuropathy has been seen in higher rates in those diagnosed with arterial hypertension, multiple sclerosis, Charcot-Marie-Tooth neuropathy, and glossopharyngeal neuralgia (38). The nature of pain is commonly severe electric shock, stabbing pain lasting from < 1 second to 2 minutes. Pain can follow from an innocuous stimulus at the trigeminal nerve distribution (20).

First-line treatment usually is carbamazepine with additional neuropathic pain agents added as needed. Carbamazepine and oxcarbazepine are first-line treatments and have great efficacy in patients with paroxysmal pain; however, these medications often lead to side effects that lead to a reduction in use by 27% and 18% of responding patients, respectively (39). Further invasive therapy can be undertaken with trigeminal nerve blocks, chemical or radiofrequency denervation, and even intracranial microvascular decompression (40).

Another similar condition includes painful trigeminal neuropathy that is defined as pain in one or more branches of the trigeminal nerve caused by another disorder with likely neural damage. This pain is often near-continuous and described as burning or squeezing. In

comparison to TN, there are less brief pain paroxysms. PHN is commonly seen in the trigeminal nerve distribution. It is more common in the elderly than younger individuals, and most commonly affects the ophthalmic division when causing facial pain. It can be treated with tricyclic antidepressants or anticonvulsants. Neurolytic treatments are not recommended because of the risk of deafferentation pain (41). Although the Neuromodulation Appropriateness Consensus Committee has not recommended the use of peripheral nerve stimulation (PNS) for trigeminal face pain (4), it may warrant consideration when intractable facial pain or headache can be localized to a specific nerve distribution.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is a rare condition associated with paroxysmal pain in the distribution of the glossopharyngeal and vagus nerve. Studies have shown an incidence of 0.9 per 100,000 per year in men and 0.5 per 100,000 per year in women, with a mean age of onset of around age 64 years. Although rarer than TN, glossopharyngeal neuralgia has also been associated with multiple sclerosis (38). Based on International Headache Society classification, the condition involves stabbing pain in the ear, base of tongue, tonsillar region, or the angle of the jaw (42). Symptoms can also involve an autonomic component with bradycardia and syncope episodes (43). Pain of a sharp, electrical nature commonly lasts from a few seconds to minutes. Swallowing, talking, coughing, or yawning often exacerbates this severe pain (20). Causes can be primary and idiopathic or secondary due to compressive lesions such as tumors, soft tissue and bone, or vascular structures (42). Neurovascular compression of the glossopharyngeal nerve may be diagnosed on imaging (20).

Medical treatment involves anticonvulsants, membrane stabilizers, and antidepressants for neuropathic pain. Nerve blocks can be performed at various branches of glossopharyngeal nerve or vagus nerve, however, their efficacy has been questioned. A randomized, prospective, active-controlled, parallel group study showed similar efficacy in treatment between 15 patients with glossopharyngeal neuralgia treated with standard oral therapy of gabapentin, tramadol, and methylcobalamin and the intervention group that received the same oral therapy with additional extraoral glossopharyngeal nerve blocks. Each patient received a diagnostic block with lidocaine followed by alternating day steroid plus bupivacaine for 3 injections and followed by 2 more blocks of only

bupivacaine. This study lacked image guidance to confirm ideal target of injectate. Although nerve blocks did not appear to add benefit, there were no adverse events, and in refractory cases nerve blocks should still be considered (44).

Surgical treatment involves rhizotomy or nerve section, or microvascular decompression of the glossopharyngeal or vagus nerve (45). A meta-analysis by Lu et al (46) of 792 patients with glossopharyngeal neuralgia treated surgically either by nerve section (36%), microvascular decompression (56%), or stereotactic radiosurgery (8%) concluded a complete long-term (median 33, 56, and 45 months, respectively) pain relief in 91% overall (96%, 90%, and 82%, respectively). Other studies show surgical treatment has great efficacy; however, temporary nerve deficits can be seen in 20 to 34% of patients with permanent damage in up to 17%. Recently, Gamma Knife radiosurgery has been proposed as a less invasive option. In one case series, 8 of 9 patients underwent a total of 10 Gamma Knife radiosurgeries targeting the glossopharyngeal meatus of the jugular foramen. A total of 8 patients reported pain relief, with 6 patients pain-free at 3 months and at 46 months on average long-term follow-up (47). Currently, there is no literature to support management of this condition with neurostimulation.

Eagle's Syndrome

Eagle's syndrome is a condition with 2 subtypes causing orofacial pain (48). Usually after a tonsillectomy, "classic type" presents with a foreign body sensation in the throat, dysphagia, frequent swallowing, and pain referred to the ear and TMJ region. Dr. Eagle hypothesized that this was due to scar tissue compressing and stretching nerve structures around the styloid process (49). "Carotid type" Eagle's syndrome occurs when an elongated styloid process impinges on the carotid artery. This can involve either the external carotid only or the internal carotid as well. Symptoms are usually exacerbated by turning the head toward the affected side (49). Some 4% to 7.3% of the general population are found to have an elongated styloid process and of this small cohort only 4% to 10.3% will present with pain. Eagle's syndrome disproportionately affects women and the elderly (50). Several mechanisms have been proposed for the etiology of pain including pressure on surrounding structures, compression of adjacent nerves primarily the glossopharyngeal nerve, lower branch of the trigeminal

nerve or chorda tympani, degenerative changes at the tendinous stylohyoid insertion, or irritation of the sympathetic nerves through impingement of the carotid vessels (51). Currently, Eagle's syndrome is defined as unilateral headache that includes neck, pharyngeal, and/or facial pain that is the result of inflammation of the stylohyoid ligament. Because of the mechanical nature of injury, pain is often instigated by palpation of the stylohyoid ligament or by head turning (20). Usual treatments range from conservative management with systemic analgesics, to local steroid infiltration, and even surgical intervention (50). Although successful management of Eagle's syndrome with PRF treatment has been reported (52), there remains little data to support management of this condition with neurostimulation. Styloidectomy is considered the treatment of choice (53).

Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) is a trigeminal autonomic cephalgia that is both underreported and underdiagnosed according to a recent review (54). Prevalence is suggested to be approximately 2 to 20 per 100,000. Age of onset is generally 30 to 40 years, affecting both men and women equally. Some 10% of cases display a clear trigger mechanism with the most common being neck movement. Only approximately 20% of PH behave episodically, and many of these ultimately end up developing into a chronic form in which attacks occur for > 1 year with remission periods of < 3 months in between (23). Patients commonly present with 5 to 40 attacks per day lasting 2 to 30 minutes each (20). It most commonly affects the temporal region in a unilateral fashion and is associated with typical cranial autonomic symptoms, such as lacrimation, conjunctival injection, or rhinorrhea. The occipital region may be involved in up to 40% of cases. Neck and shoulder pain may be present in up to one-third of cases (55). A distinguishing feature of PH is resolution of symptoms with indomethacin. However, a subset of patients has been identified in which symptoms are severe and do not respond to indomethacin or other pharmacologic interventions (54). One case report using a sphenopalatine endoscopic ganglion block with local anesthetic and steroid demonstrated significant frequency and pain relief in a patient who was unresponsive to conservative treatment (56). In these refractory cases, transcutaneous stimulation of the vagal nerve (57) and neuromodulation of the GON or SPG may be an option (54).

CONVENTIONAL TREATMENT FOR CRANIOFACIAL PAIN

Numerous treatments have been described for craniofacial pain. Although many have the potential for excellent outcomes, a substantial number of patients regularly cycle through treatments never achieving permanent success. Often headaches are sparked from certain known triggers; the first steps are to avoid these stimuli. Patients should limit caffeine, nitrates, alcohol, monosodium glutamate, aspartame, stressful situations, poor sleep hygiene, dehydration, and bright lights (58). When pain continues despite these methods, medical treatment is indicated.

Pain Medication

Traditionally oral medications are first-line treatment because of their ease of use and relatively adequate risk profile. For general neuropathic pain, first-line drugs include tricyclic antidepressants, for example amitriptyline, serotonin-norepinephrine reuptake inhibitors such as duloxetine or venlafaxine, and anticonvulsants such as gabapentin or pregabalin. Medications with a weaker grade of recommendation include oral tramadol, capsaicin patches, and lidocaine patches. Patients regularly find themselves on multiple medication regimens and often trialing new classes as relief is unsatisfactory. However, there are some conditions that have shown positive outcomes with specific medications. For instance, the anticonvulsant carbamazepine has displayed positive efficacy in TN (59). In addition, the nonsteroidal anti-inflammatory drug (NSAID) indomethacin has excellent efficacy in patients with PH (54).

Regarding headaches, treatment often focuses on either abortive or prophylactic therapy. Abortive medications are taken after a migraine attack has already commenced, whereas prophylactic treatments are designed to either minimize the intensity or frequency of the regularly experienced headaches. Abortive treatments include triptans and other 5-hydroxytryptamine agonists that have vasoconstricting properties. Oxygen therapy is often used when accessible in settings of acute attacks. Butalbital can be combined with caffeine and acetaminophen or aspirin. NSAIDs may have effectiveness in mild to moderate migraine pain. A short course of steroids can also provide relief. Overall, narcotics should be avoided whenever possible. For prophylactic treatment, beta-blockers are frequently used and have shown good efficacy. Anticonvulsants, antidepressants, and antihypertensives, such as candesartan or lisino-

pril, have been commonly trialed. Studies have shown that taking these medications > 10 times per month over a prolonged period of time can lead to negative consequences from the medications themselves, or worsening of headaches through rebound headache syndrome. Furthermore, these medications often have a delayed onset that limits their action in acute attacks. Because of this lag time, many treatments have focused on preventing the number of attacks (58).

Physical Therapy

Similar to most chronic pain syndromes, physical therapy (PT) can offer therapeutic benefit. PT has been mostly studied in migraine patients and has been shown to increase the patient's perception of change and overall satisfaction to migraine treatment. PT has been demonstrated to reduce nociceptive afferents in the craniocervical region (60). Although there remains limited evidence suggesting PT or aerobic exercise improves frequency or duration of headaches, PT remains a useful tool with minimal risk and possible improvement in overall pain intensity (61).

Psychological Treatment

A holistic approach often includes behavioral therapy. Biofeedback has shown positive outcomes in treating tension and migraine headaches. Biofeedback allows the patient to be informed on the physiologic process that is occurring, bringing the patient new awareness on their condition. In theory, the patient will be able to use this knowledge to learn how to voluntarily control the previously involuntary processes of pain. Feedback is often provided through electromyography in various muscles or through topical temperature readings (62).

Cognitive-behavioral therapy takes advantage of the link between emotional factors and pain. Therapy usually includes relaxation training, operant conditioning, and focusing on specific attitudes and beliefs that may trigger behavioral or emotional pain responses. Social support groups have proven to be beneficial in patients with chronic pain, including migraine (62).

Acupuncture

Acupuncture has been trialed in areas of the head and face. For TN, acupuncture has shown to reduce severity of attacks (63). In addition, several studies have concluded that acupuncture treatment may be beneficial when compared with current prophylactic drug therapy in preventing and treating both migraine and tension headache (64).

Trigger Point Injection

Although common in clinical practice, there is little data on the efficacy of trigger point injections for treatment of craniofacial pain. There is no defined optimal drug regimen or injection schedule (65). In patients with tight or tender muscles, routine trigger point injections may provide some symptomatic relief.

Botulinum Toxin Injection

Injections with onabotulinumtoxinA in the pericranial muscles has been approved for CM headaches since 2010 by the US Food and Drug Administration. Diener et al (66) described the technique of 31 separate fixed-site intramuscular injections each delivering 5 units of onabotulinumtoxinA for a total dose of 155 units. The injections were divided over 7 defined head and neck muscle areas: corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal and trapezius. Depending on the patient's symptoms, an additional 40 units may have been given to the occipitalis, temporalis, and/or trapezius muscle groups. After 2 cycles separated by 12 weeks, there were positive outcomes including reduction in disability and improvement in function, vitality, and quality of life. The authors conclude onabotulinumtoxinA is effective for prophylaxis of headache in adults with CM. A recent review of guidelines reports onabotulinumtoxinA is safe and effective for reducing the number of headache days in patients with CM, but is ineffective for patients with episodic migraine and is probably ineffective for treating chronic tension-type headaches (67). In addition, botulinum toxin has been trialed for facial nerve pain and spasms, such as in TN, however, larger studies are required (58).

Nerve Block

Local anesthetic and steroid injections are often used to target specific nerves. These treatments often have short-lasting responses and require frequent repeat injections. At times, relief may last from weeks to months because of a response in central pain modulation. Common targets include the GON, LON, and trigeminal nerve including its supratrochlear, supraorbital, and auriculotemporal branches. These procedures can be performed using anatomic landmarks or image guidance including fluoroscopy or ultrasound. Although there are few well-controlled trials, the greatest evidence is for greater occipital blocks in patients with CH (68). Furthermore, temporary nerve blocks can aid in establishing the diagnosis.

SPG Block

The SPG has been specifically targeted as it contributes to the autonomic response displayed by many craniofacial pain syndromes (69). There is moderate evidence for the use of SPG blockage to treat CHs with cocaine or the preferred lidocaine. The addition of steroids may extend relief, however, evidence is weak. For migraines, one study demonstrated significant relief lasting 24 hours with bupivacaine application. Similarly, lidocaine nasal spray has been effective to treat TN. Although SPG block has efficacy acutely, there remains a lack of evidence for chronic pain management (70).

Radiofrequency Ablation

Radiofrequency ablation (RFA) uses heat energy to create tissue destruction and loss of myelinated fibers, thus creating the ability to provide longer pain relief when compared with local anesthetic and steroid blocks. RFA has strong evidence when targeting the SPG when treating intractable CHs (69). Observational cohort studies report short to intermediate pain relief in occipital neuralgia (27). Similarly, in patients with TN, RFA of the Gasserian ganglion has displayed positive outcomes. Of note, longer pain relief was observed in patients with mandibular division pathology compared with those with maxillary branch or multiple distributions of pain (71). PRF works by induction of a low-intensity electrical field around sensory nerves that causes an overall decrease in conduction and an inhibition of long-term activation without associated thermal coagulation seen with standard RFA at higher temperatures. Recently, PRF of the Gasserian ganglion was shown to be an effective, safe and nondestructive method for those patients with intractable TN (72).

Chemical Neurolysis and Chemodenervation

Neurolysis of any nerve can be achieved through conventional radiofrequency, electromagnetic field PRF, or chemical neurolysis with phenol and alcohol, or more commonly glycerol. Neurolysis of the Gasserian ganglion has been used for TN and CHs (73). The most common complication includes facial hypoesthesia for > 2 weeks. Rare complications, from 0% to 2%, are cranial neuropathies and bacterial meningitis (74). Another option is percutaneous microcompression using a balloon catheter to compress the Gasserian ganglion. Neurolysis of the SPG has shown promise in treating patients with sphenopalatine neuralgia, TN, CH, migraine, and other atypical facial pain. The SPG is targeted through an infrazygomatic approach (73).

Intravenous Transfusion

Intravenous lidocaine has been thoroughly studied in patients with chronic pain. Retrospective cases have demonstrated promise using intravenous lidocaine in chronic daily headache. In patients with PHN, intravenous lidocaine has displayed significant improvements in pain scores. Further studies are indicated for intravenous therapy including lidocaine, ketamine, and phentolamine (75).

Surgery

Surgery can successfully relieve irritation of a nerve or can provide relief through nerve resection. Microvascular decompression has shown success in patients with TN when a neighboring vessel, usually the superior cerebellar artery, is responsible for compression of the nerve root. If no compressing vessel is identified, internal neurolysis may be performed that divides the nerve into 8 to 10 bundles from the pons to the petrous bone (74). Pain relief can also be achieved through intentional direct injury to or disruption of the offending nerve. In addition to the inherent risk of invasive surgery itself, destruction of a nerve may increase the risk of developing difficult to treat pain conditions such as causalgia or neuroma formation (27).

Another procedure, nucleus caudalis dorsal root entry zone ablation has reported good outcomes in treating refractory TN, atypical headache, and complex craniofacial pain. The trigeminal nucleus caudalis has been described to receive and integrate nociceptive sensation. This procedure is performed under open surgery as the substantia gelatinosa at the nucleus caudalis level is lesioned. Because of the risks of damage to the brainstem during surgical manipulation, this procedure is often a last resort. Another technique, trigeminal tractotomy and nucleotomy involves lesioning the descending spinal trigeminal tracts in the medulla along with the nucleus caudalis. Surgical procedures are reserved for intractable severe cases (74).

Gamma Knife Radiosurgery

Gamma Knife radiosurgery has been developed for the treatment of nerve pain such as TN. This technique involves radiation of the trigeminal nerve usually 2 to 4 mm anterior to the brainstem. Studies have shown this technique to have excellent efficacy after a lag period of a few months. This technique is hopeful to provide relief with limited complications (63).

CRANIAL TARGETED NEUROMODULATION TECHNIQUES

Transcranial Direct Current Stimulation

Transcranial direct current stimulation involves applying weak electrical currents over the scalp. By specifically placing one electrode over a target area, the cranial neuronal firing may be either increased or decreased. A recent review suggests there is low to moderate evidence for transcranial direct current stimulation to promote pain control and reduce pain medication intake in migraineurs (76).

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation is a form of noninvasive neurostimulation focusing changes in magnetic fields to deep brain targets in hopes of upregulating or downregulating certain neural activity. For pain, the primary targets investigated include the primary motor cortex and the dorsolateral prefrontal cortex. Some success with minimal risk has been reported in patients with migraine and TN, however, efficacy has not proven to be consistent (77).

Deep Brain Stimulation

Deep brain stimulation involves placing electrical devices intracranially and targeting subcortical regions. Several studies have displayed positive results in patients with chronic pain by targeting deep brain structures including the sensory thalamus, periaqueductal and periventricular gray, and the anterior cingulate cortex. Because of the severity of possible complications, deep brain stimulation is only recommended after exhausting other modalities (78).

LEVELS OF EVIDENCE

When reviewing the available literature, it is crucial to define the overall level of evidence a study provides before the research conclusions can be adopted to clinical practice. A concrete protocol is needed when analyzing studies to create evidence-based guidelines. Manchikanti et al (79) has developed an interventional specific pain management instrument used in assessing the methodologic quality of trials (Table 1). Traditionally, randomized controlled trials (RCTs) are generally considered to be superior evidence than studies without randomization and without controls. The lowest levels of evidence are obtained from observational-based clinical experience or reports of expert committees. Using this qualified modified approach to grading of evidence, we are better able to put the totality of evidence into perspective (79).

Table 1. *Qualified Modified Approach to Grading of Evidence*

Qualified Modified Approach to Grading of Evidence (79)		
Level I	Strong	2 or more relevant high quality RCTs for effectiveness, or 4 or more relevant high quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level II	Moderate	At least 1 relevant high quality RCT or multiple relevant moderate or low quality RCTs, or at least 2 high quality relevant observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level III	Fair	At least 1 relevant high quality nonrandomized trial or observational study with multiple moderate or low quality observation studies, or at least one high quality relevant observation study or large case series for assessment of preventative measures, adverse consequences, effectiveness of other measures.
Level IV	Limited	Multiple moderate or low quality relevant observational studies, or moderate quality observation studies or large case series for assessment of preventative measures, adverse consequences, and effectiveness of other measures.
Level V	Consensus based	Opinion or consensus of a large group of clinicians for effectiveness as well as to assess preventive measures, adverse consequences, effectiveness of other measures, or single case reports.

NEUROMODULATION FOR HEADACHES AND FACIAL PAIN: EVIDENCE AND RATIONALE

Peripheral Nerve Stimulation

Although intractable pain of the trunk and/or limbs has been the traditional indication for neuromodulation via spinal cord stimulation (SCS), refractory facial and headache pain has been shown to respond to neurostimulation in some cases. When conservative medical management fails and surgery is not appropriate, has failed, or is contraindicated, neurostimulation can be a viable alternative (4). Various targets and techniques have been employed using neuromodulation for facial and headache pain (Table 2). However, PNS for facial pain and headache is not without risk as stimulation of extracranial nerves may be more technically challenging than stimulation of peripheral nerves in the torso or extremities. Common complications include infection, skin erosion, seroma, allodynia over the lead site, as well as technical complications such as lead migration, lead fracture, and battery malfunction. Although there are not enough data to reliably compare complication rates of extracranial PNS targets, mitigation of adverse events to improve patient safety and outcomes should be of utmost priority. The same principles of appropriate patient selection that apply for traditional SCS apply for this modality. Consensus recommendations also support the consideration of neurostimulation prior to initiation of long-term, long-acting opioid therapy (4).

Trigeminal Nerve Stimulation

Although central and peripheral techniques of trigeminal nerve stimulation have been well described in literature, PNS has proved to be the safer, more

reliable option (4,80,81). Ophthalmic, maxillary, and mandibular branches of the trigeminal nerve, as well as more distal branches such as the supraorbital, infraorbital, and auriculotemporal nerves anatomically lend themselves as good targets for PNS for facial pain (4). In 2004, Johnson et al (82) reported on 10 patients treated with implanted subcutaneous pulse generators and quadripolar electrodes to stimulate the supraorbital or infraorbital branches of the trigeminal nerve. This retrospective analysis showed promising results, as 70% of patients experienced at least a 50% degree of pain relief and 70% reported a decrease in medication use up to 4 years postimplantation. Of note, all 5 patients who were originally diagnosed with posttraumatic neuropathic pain had at least a 50% pain reduction post-treatment, whereas 2 out of 4 of those diagnosed with postherpetic neuropathy had a therapeutic outcome. The overall complication rate was high at 30%, with 2 patients developing wound breakdown over the connector and another patient with discomfort associated with the tension of the extension lead during head movements, each of these 3 were later successfully managed through repeat surgical intervention.

In 2006, Slavin et al (83) reviewed prospectively collected data of 30 patients who were trialed with PNS of which 22 had permanent stimulation implant surgery for their neuropathic craniofacial pain. The targets included 4 supraorbital, 3 infraorbital, and 13 occipital nerves, with 2 patients having a combination of either infraorbital and occipital or supraorbital and occipital. Twelve patients (10 occipital and 2 supraorbital) had bilateral stimulation. A total of 16 of the 22 patients reported > 50% pain relief. Specifically, 9 patients underwent implantation for trigeminal neuropathic pain,

Table 2. Neurostimulation For Headaches Studies Reviewed.

Study	Indication and Treatment	Study Design	Methods	Outcome Measures	Results	Conclusion	Level of Evidence
Reed et al. (87) [2015]	Hemiplegic Migraine Dual SON and Occipital Nerve Stim	Case Series n=4	Retrospective analysis of 4 pts. treated with concordant, combined occipital nerve and SON stim implantation post successful 5 to 7 day trial with >50% improvement in VAS or HA freq.	HA freq, HA severity, VAS, MIDAS, drug usage, and pt. satisfaction. F/u ranged from 6- 92 mos.	It was reported average HA freq. decreased by 92% (from 30 to 2.5 days per mo.); VAS decreased by 44%, drug usage decreased by 96%.	Concordant combined occipital nerve and SON stim was preferred by pts. and suggests efficacy in treating both pain and motor aura in hemiplegic migraine pts.	Level IV Limitations: small sample size, no controls, non-randomized, open-label.
Hann et al. (88) [2013]	Chronic Migraine Dual SON and Occipital Nerve Stim.	Case Series n=14	Review of 14 consecutive pts with ONS and SONS stim implantation post successful 5 day trial with >50% pain reduction. 5 pts. implanted bilateral. 9 pts. implanted ipsilateral to symptoms.	% reduction in HA severity, resolution of neuro symptoms, VAS, postoperative functional status, and reduction in narcotic use. F/u ranged from 3 to 60 mos.	Majority of pts. reported marked improvement in HA severity and freq. (71%), resolution of associated neurological symptoms (50%), and resumption of a normal functional lifestyle (50%). Post- operative complications included lead migration (42.8%), lead site allodynia (21.4%), and infection from exposed hardware (14.2%).	Dual occipital nerve and SON stim may improve freq. of pain relief, neurological symptoms, and functional capacity in chronic migraineurs compared to ONS alone.	Level IV Limitations: single-institution, small sample size, no control group, open- label, non-randomized.
Shoenen et al. (89) [2013]	Chronic Migraine Transcutaneous SON and Supratrochlear Nerve Stim	RCT n=59 30 in treatment group 29 in sham	Double-blinded, randomized, sham-controlled trial conducted at 5 Belgian tertiary HA clinics with 30 day baseline followed by 90 day treatment of either active intervention (20 mins per day) or sham.	Mean HA days, 50% responder rate in reduction of monthly migraine days, and monthly drug usage. F/u at 45 days and 90 days.	Reported both groups with average of 20% monthly migraine decrease in 1st mo., but by 3rd mo. treatment group continued to improve to a 29.7% decrease; outperforming the sham group's 4.9%. The 50% responder rate at 3rd mo. was 26%.	SON and supratrochlear transcutaneous stim is effective and safe as a therapy to prevent migraine. Beneficial effect may be greater in pts with more frequent migraines.	Level II Limitations: excluded pts currently utilizing anti-CM treatments or who failed 3 drugs.
Vaisman et al. (90) [2012]	Intractable Trigeminal Autonomic Cephalgia SON and Supratrochlear Nerve Stim	Case Series n=5 4 diagnosed with cluster headache	Retrospective analysis of 5 pts with SON and supratrochlear implantation post successful 6 to 8 day trial with >50% pain relief.	VAS F/u ranged from 18 mos. to 36 mos. (mean of 25.2 mos.).	Reported average VAS from a mean of 8.9 to 1.6, and 3 pts. were weaned off of opioids while the other 2 decreased opioid use. All pts. reported subjective functional improvement. Of note, 2 pts required re-implantations (at 1 and 3 yrs.) due to skin erosion with repeat success.	Supraorbital and supratrochlear nerve stim may have positive outcomes in pts. with intractable trigeminal autonomic cephalgia and appears to be fairly safe.	Level IV Limitations: Observational, open-label, retrospective, no control.
Simopoulos et al. (92) [2010]	Chronic Migraine Bilateral Auriculotemporal Nerve Stim	Case Report n=1	Case report on bilateral auriculotemporal nerve stim for refractory bilateral temporal distribution pain from migraine.	NRS pain scale MIDAS F/u at 16 mos.	Reported decrease in NRS from 8-9 at baseline to 5 at F/u 16 mos. later. Function improved from MIDAS grade IV to grade II.	Auriculotemporal peripheral nerve stim may be a promising therapy for pts. with CM with pain primarily in the temporal region.	Level V Limitations: Single case, open-label. No control.

Table 2 (cont.), Neurostimulation For Headaches Studies Reviewed.

Study	Indication and Treatment	Study Design	Methods	Outcome Measures	Results	Conclusion	Level of Evidence
Saper et al. (99) [2011] ONSTIM feasibility study	Chronic Intractable Migraine ONS	RCT n=66 Adjustable stim (AS)=28 Preset stim (PS)=16 Medically managed (MM)=17 Ancillary=5	A prospective, multicenter, single-blinded, feasibility RCT evaluating ONS in CM pts. that had relief post a short-acting anesthetic block to the occipital nerve. Pts. randomly divided into 4 groups.	HA days, pain intensity, POMS, MIDAS, SF-36. Responder based on >50% reduction in HA days or ≥ 3 reduction in pain score. F/u at 3 mos.	Reported 3-mo. responder rates of 39% for AS, 6% for PS and 0% for MM. Lead migration occurred in 12 of 51 subjects.	This feasibility study offers promise that ONS is effective in medically intractable CM. More studies are needed.	Level II Limitations: small sample size, needs longer f/u.
Silberstein et al. (101) [2012]	Chronic Migraine ONS	RCT n=152 Active=105 Sham=52 Intractable CM=125	multicenter, double-blinded, controlled study used occipital nerve stim trials (>50% relief) followed by both active stim and sham implants.	VAS, HA days, MIDAS, pt. reported % of pain relief. Responder based on 50% reduction from baseline VAS F/u at 12 wks.	Reported 12 wks. responder % was not statistically significant between the active and sham groups. There was statistical significance favoring active stim in pts. that noted 10%, 20% and 30% reductions in pain. Compared to sham, active group had improvement in HA days, MIDAS, and directly reported % of HA pain relief.	While the primarily endpoint of 50% pain relief did not reach statistical significance, there was statistically significant improvements in pain, number of HA days, and function over the course of 1 year. CM pts. who have failed conservative treatments may benefit from ONS.	Level II Limitations: Failed to show primary endpoint of 50% reduction in pain.
Dodick et al. (102) [2015]	Chronic Migraine ONS	Prospective open-label long-term f/u n=133 Original Active group=90 Original Sham group=43	Additional 40 wk. open-label f/u of prior Silberstein et al. RCT that involved 12 wks. of randomization to either an active or sham group. Post 12 wks., each subject received the same active stim protocol and were followed up to 1 year post implant.	Number of HA days, pain intensity, MIDAS, Zung Pain and Distress, direct pt. reports of HA pain relief, quality of life, satisfaction and adverse events. F/u 1 yr.	Reported at 1 yr. post implant, HA days were significantly decreased. The number of pts. achieving a 30% and 50% reduction in HA days or pain intensity was 59.5% and 47.8% respectively. Of note, a total of 183 device or procedure related adverse events: 18 (8.6%) hospitalizations and 85 (40.7%) surgical interventions; 70% experienced an adverse event.	At 1 yr. f/u the authors support the promising results from the prior study (Silberstein et al.). However, due to high complication rate more emphasis should be placed on adverse event prevention.	Level IV Limitations: Only 1 year f/u; no control after the sham group began the active treatment after wk. 12.
Burns et al. (103) [2007]	Cluster Headache Bilateral ONS	Open-label Case Series n=8	Review of 8 pts. implanted with bilateral ONS to treat medically intractable CCH.	Freq., severity, and duration of attacks. F/u ranged 6-27 mos. (median of 20 mos.)	Reported 2 pts. noted a substantial improvement in % change in CCH (90% and 85%), 3 pts. showed moderate (40%, 60%, and 20-80%), and 1 pt. with mild improvement (25%).	ONS seems safe and promising for the treatment of medically intractable CHs.	Level IV: Limitations: Retrospective, comparisons, no control.
Lenaerts et al. (104) [2008]	Migraine VNS implant	Retrospective, systematic, review of cases n=10	Case series assessed 34 pts. with prior VNS implantation, and further followed the 10 pts. identified with prior CM.	Migraine freq. 3 mos. prior to implant, 3 mos. and 6 mos. post implant.	8 out of 10 of these migraine pts. reported a reduction of monthly freq. by at least 50% in the first 3 mos. post VNS surgical implantation	VNS may have a prophylactic effect on migraine and further studies should be pursued.	Level IV Limitations: recall bias, small series, no control

Table 2 (cont.). Neurostimulation For Headaches Studies Reviewed.

Study	Indication and Treatment	Study Design	Methods	Outcome Measures	Results	Conclusion	Level of Evidence
Mauskop et al. (105) [2005]	Chronic Migraine and Cluster Headache VNS implant	Case Series n=6 4 CM 2 CH	Case series reported on 6 pts. with intractable HAs that underwent left VNS implant.	Freq. of migraine, migraine symptoms, MIDAS. F/u 4 to 18 mos.	2 out of 2 CCH pts had good results with VNS and 2 out of 4 pts. with CM reported excellent relief, while the other 2 had poor efficacy.	VNS may have efficacy in treating intractable CM and CHs; further trials are warranted.	Level IV Limitations: small series, no control.
Cecchini et al. (106) [2009]	Chronic Migraine VNS implant	Case series n=4	Pts. with severe drug-refractory daily HA and depression for at least 2 years were evaluated.	HA diary, VAS, MIDAS, HRSD28, drug usage. F/u 4 to 14 mos.	2 of the 4 pts. improved for both HA and depression at 1-3 mos. post implant	There may be a beneficial effect of chronic VNS on both drug-refractory CM and depression.	Level IV Limitations: small series, no control.
Silberstein and Mechtler et al. (107) [2015]	Episodic Cluster Headache and Chronic Headache tVNS	Randomized, double-blind, sham-controlled study n=133 60 in treatment group 73 in sham	CH pts. randomized into treatment and sham groups. At start of HA feelings, pts. instructed to manually deliver 3 consecutive 2-minute stims to the right side of the neck. After this 1 mo. phase pts entered 3 mos. of open-label use.	Pain intensity diaries, attack duration, rescue drug, adverse events, device perceptions. F/u at 1 mo. to 4 mos.	In those previously diagnosed with ECH there was a positive response rate (34.2% vs 10.6% in sham group), defined as the percent of pts. with a pain score of 0 or 1 on a 5-point scale. However, in the total population no significant difference between sham and treatment groups was established.	Noninvasive vagal nerve stim may best treat those with ECH as displayed with relief at 15 mins and sustained through 60 mins. However, tVNS was not effective to treat CCH.	Level II Limitations: Overall results show no benefit due to the cohort of CCH pts that did not improve.
Silberstein and Calhoun et al. (108) [2016]	Chronic Migraineurs tVNS	Prospective, multicenter, double-blind, randomized, sham-controlled n=59 30 in treatment group 29 in sham group	Adults with CM were randomized to tVNS or sham treatment for 2 mos.. After subjects receiving 6 mos. of open-label treatment.	Number of HA days, drug usage, safety, satisfaction and tolerability. F/u at 2, 4, 6, and 8 mos.	There was no statistically significant difference at 2 mos. Following this, 27 pts. completed 6 mos. of open-label treatment. At mo. 8, for the 15 pts. who completed treatment the reduction in HA days was 7.9 and reached statistical significance. At 6 mos. 38.5% and at 8 mos. 46.7% of pts. achieved > 50% response.	Therapy with tVNS is well tolerated and in pts. with CM there may be benefit in reducing number of HA days from persistent prophylactic use.	Level II Limitations: There was a high loss to f/u, thus reducing sample size, and possibly introducing error.
Gaul et al. (109) [2015]	Chronic Cluster Headache tVNS	Prospective, open-label, randomized n=97 tVNS and standard of care (SoC) group SoC group	CCH pts. after a 2 wk. baseline were randomized to a 4 wk. SoC plus tVNS or a control (only SoC). This was followed by another 4 wk. extension phase of SoC plus tVNS.	Number of CH attacks per wk., response rate, HIT-6, EQ-5D-3L, abortive drug, and safety/tolerability. F/u at baseline and at 2 wks. and 6 wks.	Reported statistically significant reduction in number of attacks per wk. in tVNS group with a mean of 3.9 fewer attacks than the control group. For response rate higher than 50%, SoC plus tVNS was superior (40%) compared to SoC alone (8.3%).	Adjunctive prophylactic use of tVNS has superior outcomes, including reduced freq., compared to those using SoC alone. Furthermore, it is well-tolerated.	Level II Limitations: lack of placebo, short-study time.
Tso et al. (57) [2017]	Paroxysmal Hemiparesis tVNS of the Cervical Branch	Case Series n=6 3 pts. tVNS plus indomethacin, 3 pts. tVNS without adjunct indomethacin.	6 pts. with PH were treated with tVNS. Dosing regimens ranged from 2 to 4 doses twice daily, or 2 to 3 doses 3 times daily.	Freq. severity F/u 3 mos. to 5 yrs.	4 of the 6 reported benefits in either freq. or severity from this treatment ranging from 3 mos. to 5 yrs. Of the 4 responders: 1 pt. became attack free, 2 reported a reduced attack freq., 3 reduced severity, and 1 shorter duration.	tVNS may be a promising alternative or adjunct therapy for pts. with PH who are unable to tolerate indomethacin.	Level IV Limitations: small sample, no control.

Table 2 (cont.), Neurostimulation For Headaches Studies Reviewed.

Study	Indication and Treatment	Study Design	Methods	Outcome Measures	Results	Conclusion	Level of Evidence
Straube et al. (110) [2015]	Chronic Migraine tVNS of the Auricular Branch	Prospective, double-blind, randomized, parallel-group, controlled trial n=39, 22 pts (25 Hz), 17 pts (1 Hz)	CM pts. at one site underwent a 4 wk. baseline period followed by a 12 wk. randomized trial with either 25 Hz or 1 Hz tVNS for 4 hours per day.	HA days, drug usage, HIT-6, MIDAS. F/u 2, 4, 8, and 12 wks.	29.4% of the 1 Hz group had at least a 50% reduction in HA days compared to 13.3% of the 25 Hz group. Surprisingly, the 1 Hz group outperformed the 25 Hz (which is the routine freq.).	tVNS may be a safe alternative to trial in CM, however more studies are needed specifically to define ideal stim parameters as in this trial 1 Hz was more effective.	Level II Limitations: study was designed with the 1 Hz group to act as a control.
De Agostino et al. (111) [2015]	Refractory Chronic Migraine HCSCS	Case series n=17	This retrospective survey reports the use of HCSCS in pts. with medically intractable CM.	Pain intensity, HA days, quality of life, pain drug usage. F/u range 2-48 mos. (median of 15 mos.).	Reported pain intensity reduced by 60% overall, with 71% of pts. displaying a ≥ 50% decrease. Number of HA days, quality of life, and pain medication usage all showed statistically significant improvements.	High-cervical spinal cord stim is promising for pts with refractory migraine as it may improve pain and quality of life.	Level IV: Limitations: retrospective, small survey, no control.
Wolter et al. (114) [2011]	Intractable Chronic Cluster Headache HCSCS	Prospective Case Series n=7	This case series examines HCSC in pts. with CCH post successful test phase of 4-19 days.	Attack freq., duration, and intensity. HADS, PDI, pain med use. F/u range 3-78 mos. (mean 23 mos.)	Reported attack freq. reduction of 40%, as well as statistically significant reduction in duration and intensity with effects lasting for 3 to 78 mos. with a median f/u of 12 mos.	High-cervical spinal cord stim demonstrates an effect size comparable or larger to those described with ONS in treating pts. with intractable CCH.	Level IV: Limitations: small series, no control.
Arcioni et al. (115) [2016]	Refractory Chronic Migraine HF10 HCSCS	Prospective, open-label, exploratory study n=14	This prospective study assesses HF10 HCSCS for treatment of medically intractable CM post successful 2-4 wk. trial with >50% relief.	HA intensity (NRS) and number and duration of episodes. MIDAS, HIT-6, SF-12. F/u monthly until 6 mos.	Reported 50% to have >30% reduction, and 35% had >50% decline in HA days. Overall, 8 subjects reverted to an episodic pattern with HA < 15 days a mo. 1 pt. required surgical revision secondary to lead migration.	Paresthesia-free cervical HF10 SCS may be a safe and promising treatment for medically refractory chronic migraineurs.	Level IV Limitations: small series, open-label, no control.
Lambru et al. (116) [2016]	Intractable Headache Disorder HF10 HCSCS	Retrospective Case series n=7 4 with CM with CCH with SUNA	Case series assessing HF10 HCSCS in pts. with intractable HA disorder post successful 2 wk. trial with >50% relief.	HA freq., duration, severity, medication usage, and HIT-6. Follow-up range 12-42 mos. (average 28 mos.).	4 chronic MG and 2 SUNA pts. all reported > 50% reduction in HA freq. and/or intensity. The CCH pt. reported a significant reduction in attacks duration. Of note 2 pts. had lead migration.	HF10 SCS has promising long-term safety and efficacy results in pts. with chronic refractory primary HA disorders.	Level IV Limitations: Retrospective, small series, no control.
Deshpande et al. (126) [2011]	Complicated Migraine and ON PNFS of temporal region and ONS.	Case report n=1	Case report describes bilateral auriculotemporal and ONS for complicated migraine and ON.	HA onset, neurological deficits. F/u at 24 mos.	Reported reduction of greater than 50% in HA onset with cessation of neurologic deficits that originally accompanied HA.	It is feasible to treat CM symptoms with combined bilateral auriculotemporal and ONS.	Level V Limitations: Single case, open-label, No control.
Verrills et al. (127) [2014]	Chronic Daily Headache, CM, and ON PNFS targeting Occipital, SON, and Infraorbital and Infraorbital Nerve Area	Prospective study n=60 50 occipital 3 SON and 7 combination of these nerves	Consecutive pts. were prospectively followed after PNFS implantation post a successful 6-10 day trial phase with >50% pain relief of their cranio-facial pain.	NRS, analgesic use, ZDI, NDI, satisfaction, and surgical complications. F/u range 3-42 mos. (average 12.9 mos.).	Reported an average drop in NPRS of 4.8, and 41 out of the 60 pts. demonstrated > 50% reduction in pain. 23 of 35 reported a moderate to extreme decrease in analgesic use at f/u. 4 pts. had explants due to complication.	PNFS targeting the occipital, supraorbital, and/or infraorbital nerves may be a promising therapeutic treatment to relieve pain in pts with intractable HA.	Level IV Limitations: Results are not reported for each individual diagnosis, no control.

Table 2 (cont.), Neurostimulation For Headaches Studies Reviewed.

Study	Indication and Treatment	Study Design	Methods	Outcome Measures	Results	Conclusion	Level of Evidence
Schoenen et al. (130) [2013] Pathway CH-1	Cluster Headache On-demand SPG Microstimulator	Prospective, multicenter, randomized, sham controlled study n=28 pts in experimental group n=566 total CH attacks	28 pts. each instructed to use the on-demand SPG stim device for 15 mins as they experienced HA. Device was programmed to randomly deliver either full, sub- perception, or sham stim for 3 wks. minimum and 8 wks. maximum or shortest period until 30 treated attacks. Then, pts. were followed open-label for 1 yr. post implant.	0-4 pain scale HA diary before and 15, 30, 60 and 90 mins after stim start, attack freq., treatment, HIT-6, SF-36v2, and serious adverse effects. F/u range 3 to 8 wks. in experimental group and f/u at 12 mos.	Out of the 566 total CH attacks treated, 67.1% of those that received full stim achieved pain relief at 15 minutes compared to just 7.5% of those that received sham treatment. 36% had ≥ 50% reduction in attack freq.. Of 32 total implants, there were 3 lead revisions and 2 explant procedures.	Patient-controlled microstimulation of the SPG is highly effective in aborting attacks in CCH and may decrease the freq. of future attacks.	Level II Limitation: During trial period no pts. received ideal regimen as sham and sub-perception stim was randomly mixed with treatment doses.
Jürgens et al. (131) [2016]	Cluster Headache On-demand SPG Microstimulator	Long-term f/u from RCT trial by Schoenen et al. n=5956 attacks n=33 total pts implanted	2 year open-label f/u of the pts. previously implanted with SPG on-demand microstimulators as part of the RCT by Schoenen et al.	CPS diary before and immediately after stim, cluster attack freq., medications, and HA disability. F/u at 18 mos. and 24 mos. post stim.	45% were acute responders as they demonstrated ≥ 50% decrease of pain in ≥ half of their attack. 35% reported a ≥ 50% reduction in attack freq. 61% were therapeutic responders as they had either an acute pain relief or freq. response.	SPG microstimulation is a fairly safe and effective therapy offering sustained efficacy over 24 mos.. More than a third of the CH pts. maintained a reduction in attack freq.	Level IV: Limitations: no control.
Barloese et al. (132) [2017]	Cluster Headache On-demand SPG Microstimulator	Prospective, open-label n=85 78 chronic and 7 episodic CH	Followed pts. in an open-label registry who were implanted for CH with SPG microstimulator.	CPS, HA freq., medication use, HIT-6, and SF-36v2 F/u 3, 6, and 12 mos.	32% were acute responders: effective therapy in ≥ 50% of their attacks and were able to treat 86% of all attacks. 68% of pts. were therapeutic responders (≥50% decrease in freq. or good relief in ≥50% of attacks).	SPG microstimulation is an effective therapy for CH pts.; reducing medication usage, reducing HA impairment, and improving quality of life.	Level IV: Limitations: no control. Retrospective self-reported data.
Schytz et al. (133) [2013]	Cluster Headache SPG either HF (80-120 Hz) or LF (5 Hz)	Double-blind, randomized cross-over study n=6	CH pts. with previously implanted SPG microstimulators were randomly chosen to receive either HF or LF stim for 3 mins. on two separate days.	CPS, HA characteristics, blood pressure, heart rate, mean middle cerebral artery blood flow velocity, oxygenated and deoxygenated hemoglobin.	3 pts. reported cluster-like attacks during or within 30 minutes of LF SPG stim and each of these attacks were successfully treated with HF stim. One patient reported cluster-like attack within 3 minutes of HF SPG, which was also successfully treated with further HF stim.	LF stim may increase efferent parasympathetic outflow from the SPG and trigger CHs which may be better controlled utilizing HF stim.	Level II Limitations: small study, short-term effects.

Abbreviations: Stimulation (stim), patient (pt.), Abbreviations: headache (HA), frequency (freq.), follow-up (f/u), Migraine Disability Assessment (MIDAS), month(mo.), Profile of Moods States (POMS), year (yr.), short form survey (SF), week (wk.), Hamilton Rating Scale for Depression (HRSD28), Headache Impact Test (HIT-6); Hospital, European quality of life group 5 dimensions 3 level (EQ-5D-3L), Hospital Anxiety and Depression Scale (HADS), Pain Disability Index (PDI); Short-lasting Unilateral Neuralgiform headache attacks with Autonomic symptoms (SUNA), Zung Depression Index (ZDI), Neck Disability Index (NDI), categorical pain scale: 0 to 4 with: 0-no pain, 1-mild, 2-moderate, 3-severe and 4-very severe (CPS).



Fig. 3. Fluoroscopic image of supraorbital and infraorbital stimulation.

and 3 of these patients had their stimulators removed each secondary to either improvement of pain, loss of efficacy, or generator site infection. Of the remaining patients, 5 out of the 6 had > 50% pain improvement over a mean 44-month follow-up period. In 2012, Stidd et al (84) presented 3 cases of patients with trigeminal neuropathic pain. The first 2 cases developed chronic facial pain in the ophthalmic and maxillary distribution posttraumatic fractures. After 7- to 10-day successful trials targeting the supraorbital and infraorbital nerves (Fig. 3), both patients underwent implantation with promising results. The third patient suffered from herpes zoster in the ophthalmic distribution. After a successful 7-day trial, the patient was implanted with supraorbital nerve stimulator. Although initial pain relief was substantial, the pain returned secondary to lead migration. After reimplantation, patient continued to report 60% pain decrease. Interestingly, one case report demonstrates optimal stimulation for facial pain using “cross talk” between one peripherally placed lead at the maxillary nerve and one cervical epidural lead (85). To be further discussed, the branches of the trigeminal nerve remain integral in targeting craniofacial pain. Although evidence for efficacy are limited case series, case reports, and expert consensus guidelines, results have been promising for intractable craniofacial pain.

Supraorbital and Supratrochlear Stimulation

Similarly, supraorbital nerve stimulation has been

shown to be effective for treatment of supraorbital neuralgias, as well as other headache disorders such as CMs and CHs (4). Amin et al (86) published a case series of supraorbital PNS in 2008. The study showed marked reduction in pain scores and opioid consumption after 10 of 16 trialed patients were permanently implanted for supraorbital neuralgias. A small case series by Reed et al (87) found that concordant combined occipital and supraorbital neurostimulation may provide effective therapy for both the pain and motor aura in some patients with hemiplegic migraine. Hann et al (88) had similar promising results in a case series involving 14 patients who underwent dual supraorbital and ONS for CMs. A majority of patients reported marked improvement in headache severity and frequency (71%), resolution of associated neurologic symptoms (50%), and resumption of a normal functional lifestyle (50%). However, 9 of the 14 experienced a postoperative complication that included lead migration (42.8%), lead site allodynia (21.4%), and infection secondary to exposed hardware (14.2%). Five patients (35.7%) needed one or more reoperations due to infection, incomplete coverage from stimulation, or near electrode exposure.

In 2013, Schoenen et al (89) reported on a randomized control sham trial on 59 patients with migraine: 30 in treatment group and 29 in sham. They used transcutaneous neurostimulation with self-adhesive electrodes placed over the skin targeting the supraorbital and supratrochlear nerves bilaterally for 20 minutes a day for 90 days (compliance was approximately 60% for daily stimulation). Interestingly, both groups reported a decrease in migraine days on average by 20% in the first month. However, at month 3, the decrease in monthly migraine days in the treatment group continued to improve to 29.7%, whereas the initial positive response in the sham group was no longer exhibited. Of note, this trial excluded patients who were using antimigraine treatments in the past 3 months and those who had failed at least 3 preventative drug treatments; these refractory patients are the seemingly helpless patients who surgical implantable stimulation regularly attempts to treat.

In 2012, Vaisman et al (90) reported on a retrospective case series of 5 patients presenting with intractable trigeminal autonomic cephalgia, 4 diagnosed with CH. After implantation of neurostimulation device targeting the supraorbital and supratrochlear nerves, patients on average reduced pain from a mean of 8.9 to 1.6 with an average follow-up period of 25 months. Of note, 2 patients required reimplantations (at 1 and 3 years)

due to skin erosion with repeat success and 3 patients were completely weaned off of opioids, whereas the other 2 decreased their opioid usage. Supraorbital nerve stimulation, which can cover the supratrochlear region as well with a single lead placement, has positive outcomes in multiple retrospective case series; further research is indicated.

Auriculotemporal Stimulation

The auriculotemporal nerve is another terminal branch of the trigeminal nerve that has been targeted with PNS. Rodriguez-Lopez et al (91) conducted a small prospective case series in 2015 for 6 patients with TMJ syndrome that did not respond to intraarticular local anesthetic or corticoid steroid injections. With PNS of the auriculotemporal nerve (Fig. 4), the group reported an average of 72% pain relief with the majority of patients discontinuing analgesic medications. One case report followed a patient treated with bilateral auriculotemporal nerve stimulators for CM. Pain intensity decreased from 8-9 to 5 at the 16-month follow-up. In addition, migraine disability assessment went from total disability to mild disability as photophobia and pain were better controlled (92). The auriculotemporal nerve has been used for targeted PNS to treat migraine headache and jaw pain with promising efficacy.

Halo 360° Cranial Stimulation

The halo 360° cranial stimulation with the unique placement of a novel device aims to provide a wide array of coverage across the bilateral head to treat headaches, primarily migraines. This technique used 4 leads each with 8 electrode contacts and all powered by one single implantable pulse generator, thus allowing for a greater number of contacts over previous devices. Bilateral leads are placed superior to the ear and anteriorly to stimulate the supraorbital, supratrochlear, zygomaticotemporal, and auriculotemporal nerves. In addition, bilateral leads are placed posteriorly to stimulate the greater and lesser occipital, greater auricular, and branches of the third occipital nerve, and the posterior rami of C2 and C3 nerve roots (93). This comprehensive method requires further investigation for efficacy.

Occipital Nerve Stimulation

ONS has been used to treat occipital neuralgia refractory to conventional medical management. Because of its mechanism and efficacy, the occipital nerve is one of the most studied targets for head and neck pain. With the greater and LONs being distal branches of C2

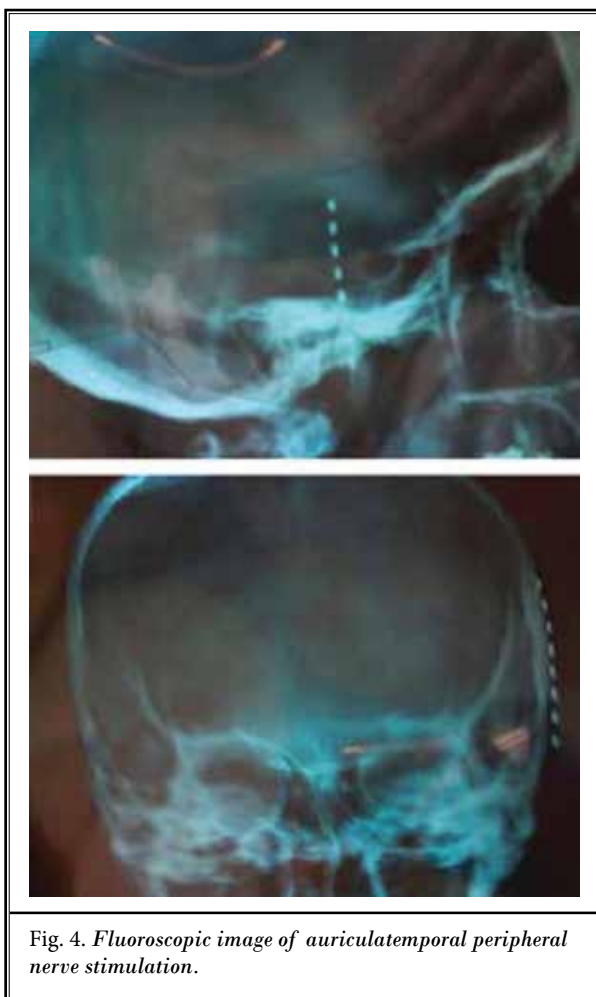


Fig. 4. Fluoroscopic image of auriculotemporal peripheral nerve stimulation.

and C3, the mechanism of action is thought to involve modulation of peripheral and central nociceptive inputs (94) (Fig. 5). Regional cerebral blood flow has also been shown to increase after ONS in migraineurs, an encouraging finding in the treatment of neurovascular headache (95).

A study looked at 10 patients being treated for drug refractory chronic CH with ONS. Cranial positron emission tomography scans of 4 chronic stimulator patients and 6 patients scanned prestimulator implantation and postimplantation demonstrated that ONS has a neuromodulator effect in the central pain matrix, suggesting that the ONS works to reduce the ipsilateral hypothalamic hyperactivity that can be found in acute episodic CH attacks (96).

One case series focusing on occipital neuralgia followed 13 patients who underwent a total of 17 peripheral suboccipital stimulation implants (Fig. 6) for

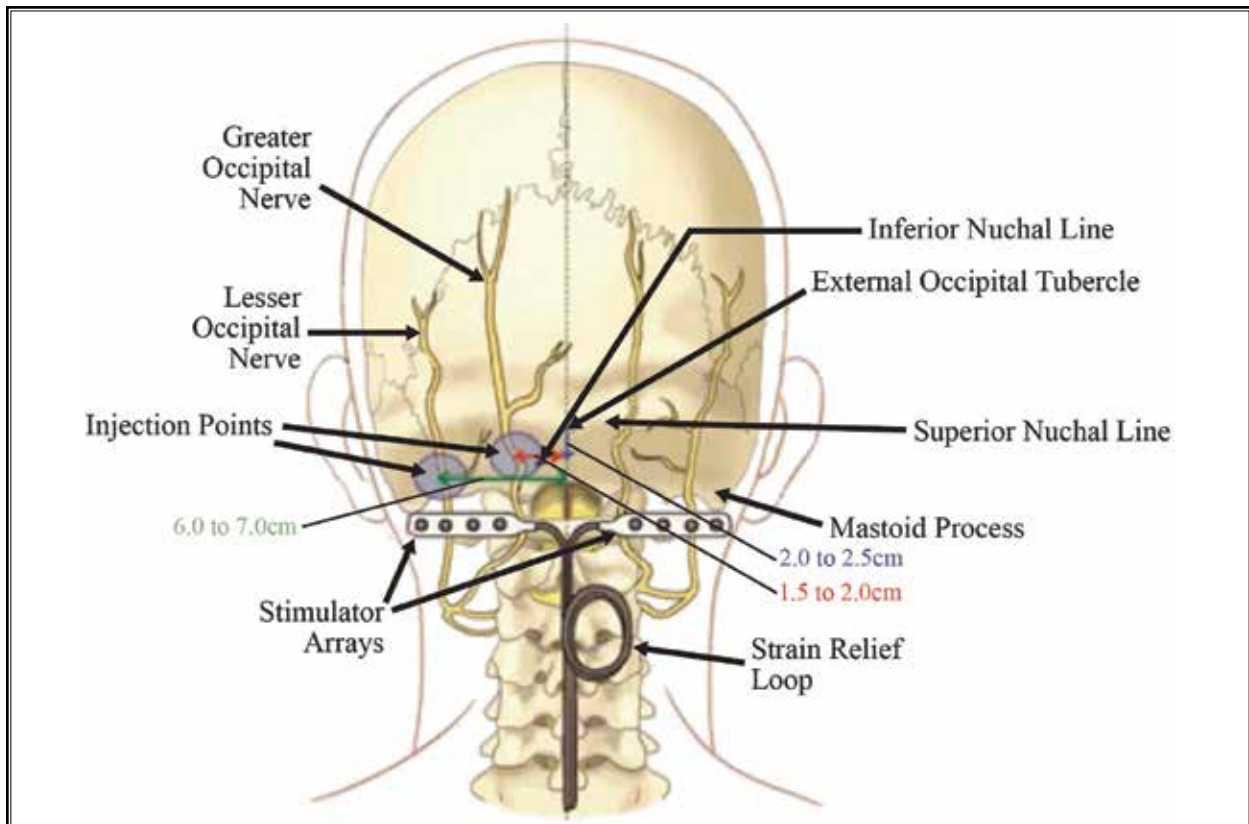


Fig. 5. Diagram of occipital nerve stimulation placement.

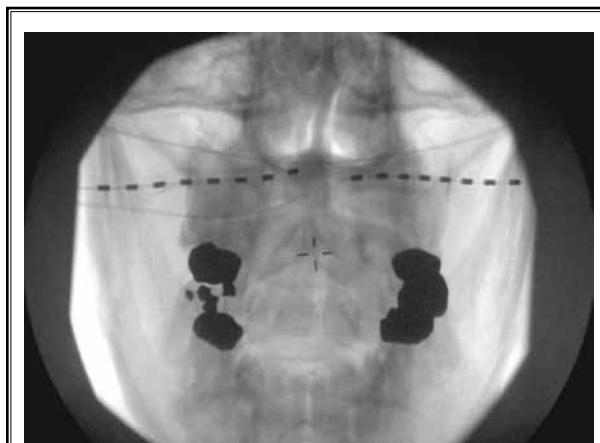


Fig. 6. Fluoroscopic image of occipital nerve stimulator.

intractable occipital neuralgia. To differentiate from migraines, each patient was required to demonstrate some response to local occipital nerve or selective C2 root block. The target for stimulation was the occipital

nerve trunk at the level of C1. In this series of cases, over an average of 2-year follow-up, 66% of patients had excellent responses reported at > 75% pain relief. The remaining 33% demonstrated good responses with at least 50% pain relief (97). Similarly, Kapural et al (98) described 6 patients with severe refractory occipital neuralgia who were treated with ONS at C1 through a midline approach. At 3-month follow-up, there was a significant change in pain and disability.

The GON has been a promising target for PNS for not only occipital neuralgia, but a variety of other painful conditions of the head and neck, including both primary and secondary headache disorders (4). Contrary to other PNS targets for head and facial pain, there have been prospective, RCTs reported on the use of ONS. The ONSTIM trial was a prospective, multicenter, single-blinded, feasibility RCT sponsored by Medtronic Inc. using ONS for chronic intractable migraine (99). Patients were randomized into adjustable stimulation (n = 28), preset stimulation (n = 16), and medical management (n = 17) groups. At 3 months after implantation, 39% of patients in the adjustable stimulation group showed

a reduction in headache days per month or a > 3 point reduction in pain scores. Of note, 24% of implanted patients were noted to have lead migration in the study. This led the authors to conclude that although the data collected were promising for the treatment of migraines using ONS, more studies are needed in this area (100).

Another prospective RCT using ONS was sponsored by St. Jude Medical (101). This multicenter, double-blinded, controlled study used ONS trials followed by both active stimulation implants and sham implants in 157 patients with 125 meeting the criteria for intractable CM. Approximately two-thirds of the patients were randomized into the active stimulation implanted group by design. The study failed to show a significant difference in the sham versus active stimulation group in the primary endpoint, a reduction in daily mean Visual Analog Scale (VAS) pain scores by 50% at 3 months. However, there was a significant difference shown between the 2 groups in patients reporting a 30% reduction of daily VAS scores. Dodick et al (102) followed this by reporting one-year data in the study. A significant reduction in number of headache days and headache disability indices were reported along with encouraging reductions in headache intensity. Unfortunately, a high number of patients (70%) suffered a postoperative adverse event, nearly half (40%) of which required surgical intervention. The authors concluded that although results support the 12-month efficacy of PNS of the occipital nerves for headache pain and disability, more emphasis on adverse event mitigation is needed in future research. A recent review and meta-analysis of ONS for CM included several additional older RCTs and 7 case series (22). It concluded that although efficacy for ONS in migraine over sham has been established, "the average effect size is modest" and "further measures to reduce the risk of adverse events and revision surgery are needed (22)."

Focusing on CHs, Burns et al (103) analyzed 8 patients who had been implanted bilaterally with ONS for control of medically intractable chronic CH. The results of this open-label, case series were promising at a median follow-up period of 20 months: 2 patients noted a substantial improvement, 3 patients showed moderate improvement, and 1 reported mild improvement. Of note the first patient was implanted on ipsilateral side to where 95% of the attacks were located, after stimulation the geographic nature of the attacks changed, and thus bilateral stimulators was placed. From then on, each patient was implanted bilaterally. During

device malfunctions, including battery depletion, the patients reported a return of symptoms. A total of 6 out of the 8 patients would recommend the procedure. Overall, these cases suggest ONS for CH is promising. Of all the neuromodulation studies involving PNS for face or head pain, the ONS currently has the greatest level of supporting evidence for treatments including migraine, CH, and occipital neuralgia.

Vagal Nerve Stimulation

Vagal nerve stimulation (VNS) has shown efficacy in various conditions with success first illustrated in epilepsy and depression. VNS affects the parasympathetic nervous system and can result in changes in blood brain flow. Although the exact mechanism is not defined, patients with epilepsy treated with VNS were noted to simultaneously have improvements in their headaches. A retrospective case series looked at 34 patients who had been treated with prior VNS, and 10 patients were identified with a prior history of migraines. A total of 8 out of 10 of these patients with migraine reported a reduction of monthly frequency by at least 50% in the first 3 months poststimulator surgical implantation. Although the frequencies of reported migraines were small leading to large percent changes and there is potential for retrospective recall bias, this study highlighted the need for further investigation (104). A series of 6 cases concluded that 2 out of 2 chronic CH patients had good results with VNS, and 2 out of 4 patients with CM reported excellent relief, whereas the other 2 had poor efficacy (105). Another case series selected 4 patients suffering from drug-refractory CM with depression for trial with implanted VNS set to 30 Hz. The authors concluded that 2 of the 4 patients improved for both headache and depression at 1 to 3 months postimplant. Clinical trials are recommended to better determine efficacy (106).

Several studies have focused on noninvasive or transcutaneous vagal nerve stimulation (tVNS). In 2016, Silberstein et al (107) reported on their use of tVNS to treat patients with either episodic (67%) or chronic (33%) CH. On initial feelings of attack, patients were instructed to manually deliver 3 consecutive 2-minute stimulations to the right side of the neck. Response was then assessed at 15 minutes. This randomized, double-blind, sham-controlled study with 60 patients in treatment group and 73 in sham group displayed in the cohort previously diagnosed with episodic CH there was a positive response rate, defined as the percent of patients with a pain score of 0 or 1 on a 5-point scale.

However, in the total population no significant difference between sham and treatment groups was established. This suggests that tVNS may best treat those with episodic CH. Similarly, in 2016 Silberstein et al (108) studied noninvasive tVNS and this time in chronic migraineurs. In this randomized, sham-controlled trial, the treatment group (n = 30) and sham group (n = 29) did not statistically differ after 2 months. Following this, 27 patients were followed through to 6 months with open-label treatment. At month 8, for the 15 patients who completed treatment the decrease from baseline in headache days was 7.9 and reached statistical significance. At 6 months 38.5% and at 8 months 46.7% of patients achieved > 50% response. Although there was a high loss to follow-up with increasing time that may lead to overrepresentation among responders or regression to the mean, this study suggests that long-term use may be necessary before migraine prophylaxis response is achieved. Gaul et al (109) analyzed 48 patients with chronic CH treated with tVNS with a control of 49 treated with standard of care. Those treated with tVNS had a statistically significant reduction in number of attacks per week with a mean of 3.9 fewer attacks than the control group. This study further suggests the efficacy of tVNS for CH. A case series examined 6 patients with PH that were treated with tVNS with regimens ranging from 2 to 4 doses given either 2 times a day or 3 times a day. A total of 4 of the 6 reported benefits in either frequency or severity from this treatment ranging from 3 months to 5 years (57).

Another study examined tVNS in patients with migraines to target the auricular nerve (a branch of the vagus) at the concha of the outer ear. This parallel-group randomized trial analyzed 22 patients who received 25 Hz stimulation and 17 patients who received 1 Hz stimulation for a total of 12 weeks. A total of 29.4% of the 1 Hz group had at least a 50% reduction in headache days. Contrary to the authors' hypothesis, the 1 Hz group outperformed the 25 Hz (which is the routine frequency commonly used in VNS implants for other conditions) (110). Overall these studies suggest that both VNS and tVNS may be safe alternatives to trial, however, more studies are needed specifically to define ideal stimulation parameters.

SPINAL CORD STIMULATION

High Cervical Spinal Cord Stimulation

The use of dorsal column stimulation in the high cervical region has been used to treat headache and

facial pain. Neurons projecting from the trigeminocervical complex to the trigeminal nucleus caudalis can be stimulated at C2-C3 (Fig. 7), potentially covering both facial and occipital pain (94). For refractory migraine headaches, one retrospective survey showed high cervical lead placement led to a decrease in pain intensity (with 71% of patients reporting a decrease of 50% or more), headache days, and medication usage at a follow-up period with a median of 15 months. However, the study size was small (n = 17), and further evidence is needed in this area (111). Cases have been reported of successful use of high cervical spinal cord stimulation (HCSCS) to treat CHs (112) and posttraumatic headaches as well (113).

After success with one patient with medically intractable chronic CH, Wolter et al (114) reported on a case series of 7 patients. In all patients, an initial lead was placed slightly paramedian ipsilateral to the pain location. The electrode was directed cranially until movement was halted by the occipital bone or the posterior arch of the atlas. Paresthesias covered root C2 and ophthalmic nerve with some maxillary branches. In 2 patients, contralateral leads were placed one at 6 months and one at 7 years both secondary to shift of CH pain location. This study concluded that all patients had statistical differences in attack frequency, duration, and intensity, and half of the patients stopped all medication postimplantation. These results are promising with an attack frequency reduction of 40%, and effects lasting for 3 to 78 months with a median follow-up of 12 months. In 2016, Arcioni et al (115) reported on a prospective, open-label, exploratory study in which 17 patients diagnosed with refractory CM underwent a trial of paresthesia-free cervical high frequency 10 kHz (HF10) SCS. The target for stimulation was the dorsal columns in the area corresponding to C2-C3 vertebral level. There was one trial failure, one trial infection, and one implant infection. The other 14 patients had successful implants that remained at the 6-month follow-up. A total of 7 out of the 14 were reported to have > 30% reduction in headache days, and 5 out of 14 had > 50% reduction in headache days. Overall, 8 subjects reverted to an episodic pattern experiencing headaches < 15 days a month. One patient required surgical revision secondary to lead migration.

Similarly, in 2016, Lambru et al (116) reported on the use of paresthesia-free HF10 SCS for intractable headache disorder. The target for continuous stimulation was also the dorsal columns at C2-C3. This population of 7 patients included 4 with CM, 1 with chronic

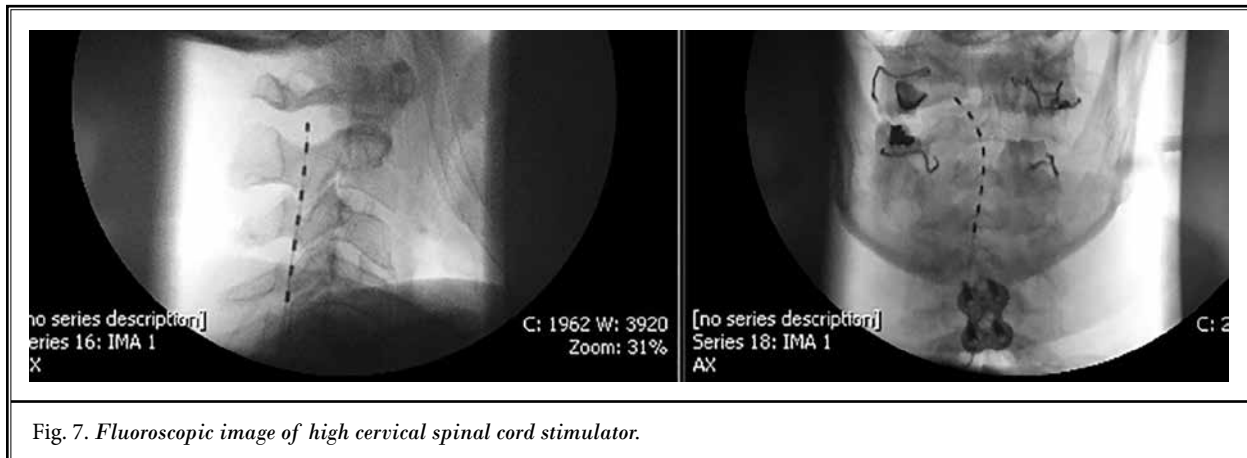


Fig. 7. Fluoroscopic image of high cervical spinal cord stimulator.

CH, and 2 with chronic short-lasting unilateral neuralgiform headache attacks with autonomic symptoms. The 4 CM patients all exhibited at least 50% reduction in headache frequency and/or intensity; the chronic CH patient reported a significant reduction in attack duration. Overall range of follow-up was from 12 to 42 months. Two patients underwent revisions secondary to lead migration. Secondary to this promising data, we are hopeful that HF10 SCS will continue to prove to be an effective headache treatment.

Reported in 2011, Tomycz et al (117) reviewed the literature for cervicomedullary junction SCS to alleviate head and facial pain. They conclude that patients with trigeminal deafferentation pain, trigeminal neuropathic pain, and PHN may respond favorably, and patients with occipital neuralgia are likely not to benefit. A single-center retrospective case series analyzed 12 patients who underwent HCSCS for facial pain syndrome (the vast majority with trigeminal neuropathy, one with TN, and 2 with neuropathic facial pain). The authors conclude that > 60% of patients had effective pain relief (118). Similarly, in 2018, Velásquez et al (119) retrospectively reported on 12 patients diagnosed with trigeminal neuropathic pain at varying and sometimes multiple nerve divisions (42% with ophthalmic, 75% with maxillary, and 33% with mandibular). Mean follow-up period was 4.4 years. The average change in Numeric Rating Scale was from a baseline of 7 to postimplantation of 3. There was a 57.1% overall pain reduction, however long-term failure rate was 25% with 2 patients not having relief and 1 patient having a late biological failure at one year. Access for implantation was performed by a midline partial C1 laminectomy to place the epidural paddle slightly lateralized to the affected side. In 75%

of patients, leads were placed at C0-C1 and in 25% the upper contact was below C1. Tonic stimulation was used in all patients. Mean follow-up period was from 0.3 to 21.1 years, with an average of 4.4 years. During this period there were a total of 19 system revisions mostly related to not ideal positioning, malfunction, or disconnection.

Furthermore, Papa et al (120) reported a case report on successfully using SCS to treat a case of refractory Eagle's syndrome to both conservative treatments and surgery. 10 KHz SCS was placed between C2 and C7. Patient's pain relief went from 10 to 4, and there was complete relief from a prior persistent foreign body sensation in the throat. Because of the patient's delayed diagnosis of over 20 years, the authors suggest the pain had become centralized. Although clearly it has been demonstrated effective in small studies and case reports, larger studies showing long-term efficacy for high cervical leads to treat headache and facial pain are lacking.

Peripheral Nerve Field Stimulation

Peripheral nerve field stimulation (PNfs) targets the subcutaneous small fiber nerve endings of peripheral nerves, not necessarily correlating with the distribution of a single "named" nerve (2). A recent cohort in 2016 of 10 patients with intractable facial pain in the trigeminal distribution who were trialed with PNfs: 8 of the 10 proceeded to implant and reported significant pain relief, and 2 of these patients reported an absence of pain after implant (121). Similar results were seen in another case series of 6 total drug-resistant patients: 2 with classical TN, 2 with concomitant persistent facial pain, and 2 with postherpetic trigeminal neuropathy. Average pain intensity decreased by

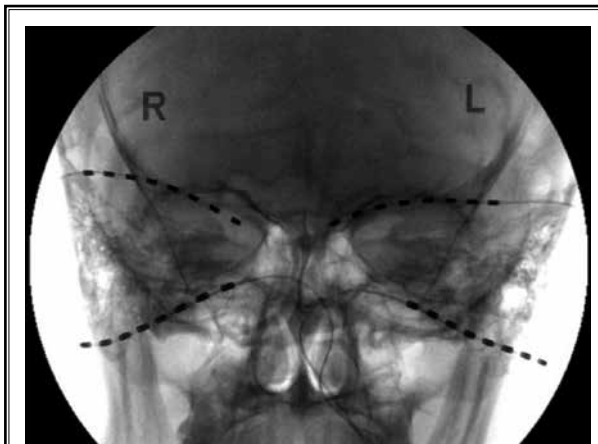


Fig. 8. Fluoroscopic image of bilateral supraorbital and occipital nerve PNfS.

83% and number of attacks decreased by 73% with a mean follow-up of 15.2 months. A total of 5 out of the 6 patients reduced their pain medication intake. One patient developed a device infection at 4 months, and after a relapse of pain underwent a second implantation that was successful. Overall, this case series shows effective treatment with PNfS for classic TN and facial pain (122).

Additional case reports have demonstrated effectiveness using PNfS for atypical facial pain (123). One patient with axial neck pain had 100% relief and reduction in opioids postplacement of PNfS to the paraspinal and trapezius muscles (124). Two PHN patients displayed successful pain relief postimplantation in the lateral thoracic region with PNfS (125). A second case report looked at combining ONS with bilateral subcutaneous electrical stimulation over the temporal region to treat a patient diagnosed with complicated migraine and occipital neuralgia. At 2-year follow-up, the headache onset was reduced by > 50%, and there was a cessation of neurologic deficits that had been seen with previous attacks (126). In 2014, Verrills et al (127) reported on 60 patients with either chronic daily headache, occipital neuralgia, or CM who underwent successful trial and later PNfS implantation with 50 targeting the occipital, 3 the supraorbital and infraorbital, and the remaining 7 were a combination of these 3 nerves (Fig. 8). Outcomes were successful with average reduction in pain scores of 4.8, and overall 41 out of the 60 patients demonstrated at least 50% reduction in pain. Although prospective trials are lacking, PNfS has shown promise as a treatment for debilitating refractory facial pain.

SPG Stimulation

Neurostimulation of the SPG is a relatively novel and promising treatment modality for refractory craniofacial pain. A 7-patient monocentric case series examined SPG and Gasserian ganglion stimulation for facial pain with most patients diagnosed with persistent idiopathic facial pain. A total of 5 of the 7 patients proceeded to permanent implantation: one patient had stimulation of the SPG; 3 patients had stimulation of SPG combined with peripheral nerve branches either the supraorbital, auriculotemporal, and occipital; and one patient had a Gasserian ganglion only implant for trigeminal neuropathic pain. A total of 4 out of 5, including several of the SPG implanted patients and the one Gasserian ganglion only implant, experienced sustained pain relief, which was reported out to 24 months, with a mean of 9.6 months (128). Of note, paresthesia-free stimulation was reported in several of the SPG stimulation cases. Due to multiple implant targets in most patients, the efficacy obtained from the SPG alone is difficult to deduce. Another case report describes successful SPG stimulation for intractable facial pain, after failure of SPG block with local anesthetic, which resulted in cessation of opioids and significant pain relief (129).

In addition to craniofacial pain, stimulation of the SPG has been well described for CH. In 2013, Schoenen et al (130) conducted a multicenter trial (Pathway CH-1) comparing on-demand ipsilateral Autonomic Technologies Inc. SPG microstimulation at HF (average 120 Hz) and subthreshold amplitudes versus sham stimulation for CH attacks. The 28 patients were implanted targeting the SPG (Fig. 9) and were instructed to use the handheld remote controller to activate stimulation for 15 minutes as needed when they experienced a moderate pain intensity headache. The devices were programmed to at different times randomly deliver each of 3 types of stimulation: full stimulation, subperception stimulation, or sham stimulation. Out of the 566 total CH attacks treated, 67.1% of those that received full stimulation achieved pain relief at 15 minutes compared to just 7.5% of those that received sham treatment. This study demonstrated statistically significant results in favor of SPG stimulation. In 2016, an open label follow-up study of the original Pathway CH-1 results showed 45% of 33 patients were acute responders as they demonstrated at least a 50% decrease of pain in at least half of their attacks through the 24-month review period. Some 35% of the 33 patients reported a 50% reduction in attack frequency, 61% were therapeutic responders as

they had either an acute pain relief or frequency response, and 30% of the patients were found to have a remission period lasting at least one month. The authors conclude that self-administered SPG stimulation is effective in the acute period, reduces attack frequency, and may induce a state of remission thereafter (131). Similarly in 2018, Barloese et al (132) reported on another open-label prospective study for 12 months in which 85 patients (78 with chronic CH and 7 with episodic CH) were implanted with a SPG microstimulator. A total of 32% of patients were acute responders meaning they had effective therapy in at least half of their attacks. These active responders were able to treat 86% of their attacks. Some 65% of all subjects were therapeutic responders in that they had 50% reduction in attack frequency or achieved effective therapy in at least half of all attacks. Quality of life scores were significantly improved at 12 months compared to baseline.

In 2013, Schytz et al (133) reported on a double-blind cross-over study in which 6 patients with CH who were previously implanted with a SPG neurotransmitter were randomly allocated to receive HF (80-120 Hz) or low frequency (LF, 5 Hz) stimulation for 3 minutes on 2 separate days. Three patients reported cluster-like attacks during or within 30 minutes of LF SPG stimulation, and each of these attacks were successfully treated with HF stimulation. One patient reported a cluster-like attack within 3 minutes of HF SPG stimulation, which was also successfully treated with further HF stimulation. This suggests that efferent parasympathetic outflow from the SPG can trigger CHs that may be better controlled using HF stimulation. HF stimulation of the SPG for

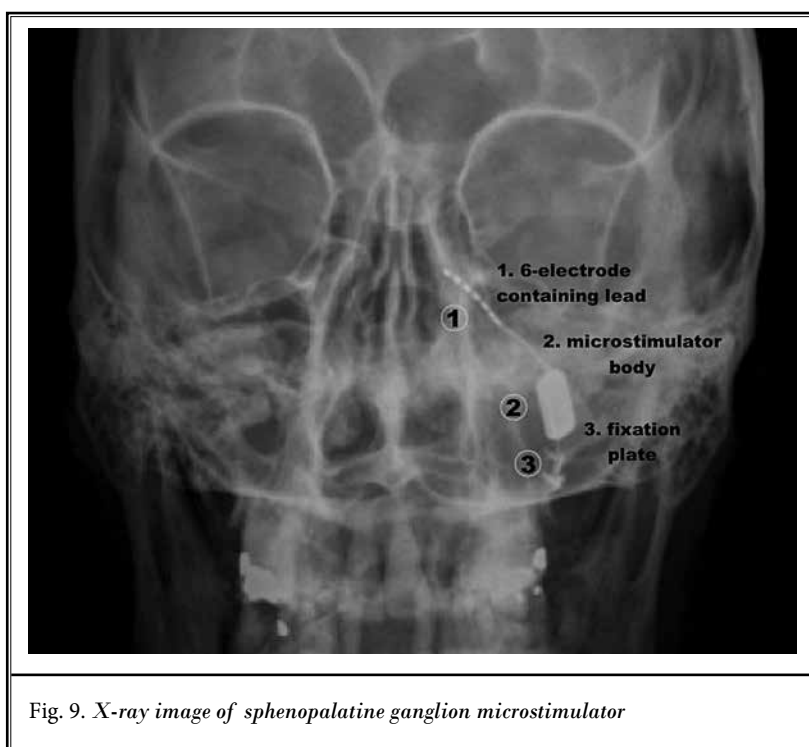


Fig. 9. X-ray image of sphenopalatine ganglion microstimulator

refractory CH is now recognized by expert consensus groups and guidelines have been published, becoming commercially available and approved in Europe (134). It appears that long-term powered prospective studies may be feasible considering that efficacy has been shown with this therapy. Studies are ongoing to evaluate the role in acute and preventive treatment of migraine headaches with SPG stimulation (135).

Gasserian Ganglion Stimulation

The Gasserian ganglion of the trigeminal nerve, as discussed, has been a target of stimulation. Reported in 1997, Taub et al (80) described a series of 34 total patients with medically intractable chronic facial pain of which 19 were treated with Gasserian ganglion stimulation postsuccessful temporary trial. Success, defined as at least 50% reduction in pain with stimulator active, was achieved in 5 of 7 patients with diagnosed central pain, 5 of 22 for peripheral pain, and none of the 4 with PHN. The authors concluded that Gasserian ganglion stimulation most effectively treated central pain from stroke. More recently, results have been increasingly favorable. The Gasserian ganglion has been a target for neuropathic pain primarily caused by infliction on the trigeminal nerve either following accidental injuries including surgical or trauma, herpes zoster infection, or a result of postinvasive ablation procedure. Kustermans et al (136) retrospectively analyzed 17 patients with refractory TN who after successful 4-week trial were implanted with a neurostimulation electrode at the level of the Gasserian ganglion. A total of 15 out of the 17 patients exhibited at least 50% pain relief postimplant. Although the pain relief decreased from 6 to 24 months, the authors conclude 44% of patients maintained long-term pain

relief after 24 months. Therefore Gasserian ganglion stimulation is promising and should be considered prior to invasive treatments such as motor cortex stimulation or deep brain stimulation.

Future Treatments on the Horizon

With advancing technology, new devices have been developed that are smaller and take advantage of wireless capabilities. This allows for the implantation of tiny leads without the need for a larger implantable power source. One case report describes efficacy of a supraorbital implantation of 2 octopolar wireless neurostimulators with an external pulse generator for a patient with posttraumatic neuralgia. Stimulation was given at HF (10 kHz) over the supraorbital nerve and patient reported a decrease in pain from 8 to 2 at both 12- and 24-month follow-up (137). In theory, a smaller wireless device can lead to a less invasive implantation and fewer complications including skin erosion, lead migration, and local pain (78).

As aforementioned, currently there are implantable on-demand wireless microstimulators that affords the patient the ability to actively control stimulation themselves, as needed. Autonomic Technologies Inc. neurostimulation is now referred to as SPG microstimulation therapy and is available in the European Union for the treatment of episodic and chronic CH. Currently, SPG microstimulation remains investigational in the United States. Pietzsch et al (138) reviewed the Pathway CH-1 study by Schoenen et al (130) and concluded that SPG stimulation has positive outcomes in patients with chronic CH and may provide an overall health care cost savings within 5 years poststimulation. Although this study assumes the results from the Pathway CH-1 study can be generalized to the entire population suffering from CH, it suggests this neuromodulation technique, while providing better health outcomes, can also simultaneously improve cost-efficacy over time.

For SCS, novel technologies are currently being tested to best therapeutically stimulate the active targets. For instance, closed-loop systems have the ability to automatically adjust stimulation levels to maximize the overall time the patient receives the optimal therapeutic dose (139). These advances have the capabilities to be adapted to treat head and facial pain. With innovative technology and an expanding knowledge base, the future for neuromodulation remains promising.

CONCLUSIONS

The nerves of the head and face form an elaborate and often interconnected network. A stimulus affecting one nerve has the ability to cause responses of nearby structures and may mimic symptomatology from other regions. Common first-line therapy primarily consists of oral medications. As many patients continue to progress to chronic states of pain, surely the current treatments are lacking. Historically, interventions such as nerve blocks and surgery served a role in this intractable population. Lately, the field of neuromodulation has become instrumental in this vulnerable subset of treatment failure patients. Neuromodulation has the opportunity to have a longer duration of relief than injections and often has a lower risk profile compared with other surgical procedures, partly owing to the reversibility of the stimulator implantation.

Many patients live with facial pain that is refractory to conservative treatment. As discussed earlier, multiple pathologies have shown positive results with PNS of various targets. For neuromodulation to be effective, the patient must be correctly diagnosed and selectively chosen so that targeted nerve stimulation can allow for a successful outcome. Larger, randomized, controlled trials are required before many of these treatments can be defined as standard of care and evidenced-based medicine. The future of craniofacial nerve stimulation is promising as advances in our overall collective knowledge, as well as in hardware and surgical technique, allow for better outcomes.

Much of the advances in neuromodulation for the head and face will stem from perfecting the techniques previously described and devising ideal treatment plans including optimizing patient selection. Some of the strongest evidence for implantable neuromodulation in facial pain includes ONS for both migraine and occipital neuralgia, and SPG microstimulation for CH (Table 3). Regarding noninvasive neuromodulation, there is positive evidence for tVNS for both migraines and CHs, as well as combined transcutaneous supraorbital plus supraorbital nerve stimulation for migraines (Table 3).

Acknowledgment

The authors would like to thank the editorial board of Pain Physician for review and criticism in improving the manuscript.

Neurostimulation for the Treatment of Chronic Head and Facial Pain

Table 3: Neuromodulation Evidence for Selected Pain Diagnosis Based on Studies Reviewed

	Migraine	Cluster Headache	Trigeminal Neuralgia	Trigeminal Neuropathy	Occipital Neuralgia	Paroxysmal Hemicrania	Glossopharyngeal Neuralgia	Eagle Syndrome	Burning Mouth Syndrome
Supraorbital	x	x	x	Level IV (82, 83, 84, 86)	x	x	x	x	x
Infraorbital	x	x	x	Level IV (82, 83, 84)	x	x	x	x	x
SON and Occipital	Level IV (87, 88)	x	x	Level IV (86)	x	x	x	x	x
SON and Supratrochlear	Level II (89) [transcutaneous stim]	Level IV (90) [lead implanted]	x	x	x	x	x	x	x
Auriculo-temporal	Level V (92)	x	x	Level IV (91)	x	x	x	x	x
Halo-Lead	Level V (93)	x	x	x	x	x	x	x	x
ONS	Level II (99, 101, 102)	Level IV (103)	x	x	Level III (83, 97, 98)	Level IV (54)	x	x	x
VNS	Level IV (104, 105, 106)	Level IV (105)	x	x	x	x	x	x	x
tVNS	Level II (108,110)	Level II (107, 109)	x	x	x	Level IV (57)	x	x	x
HCSCS	Level IV (111, 115, 116)	Level IV (114, 116)	Level V (118)	Level IV (117, 118, 119)	Level IV (117)	x	x	Level V (120)	x
PNfS	Level IV (126, 127)	Level IV (127)	Level IV (122)	Level IV (121, 122)	Level IV (121, 125, 126, 127)	x	x	x	x
Temporal PNfS and ONS	Level V (126)	x	x	x	Level V (126)	x	x	x	x
SPG	x	Level II (130, 131, 132, 133)	x	Level IV (128, 129)	x	Level V (54)	x	x	x
Gasserian Ganglion	x	x	Level IV (136)	Level IV (80, 128)	x	x	x	x	x

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