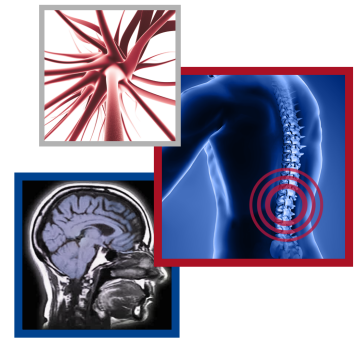
Device Evaluation

Pain Management



Device review: Pulsante™ sphenopalatine ganglion microstimulator

Nenna Nwazota[1], Srinivas Pyati[2], Kyle Fisher[1] & Lance Roy*,[1]
[1]Department of Anesthesiology, Duke University, Durham, NC 27710, USA
[2]Department of Anesthesiology, Durham VA Medical Center, Durham, NC 27710, USA
*Author for correspondence: Tel.: +1 919 662 7246; Lance.roy@duke.edu

Practice points

- Neurostimulation is a viable option for the management of drug-resistant cluster headache (CH).
- The Pulsante® microstimulator system is the first and only implantable system designed specifically for neuromodulation of the sphenopalatine ganglion.
- The Pulsante microstimulator provides effective monotherapy with dual action in decreasing both CH attack severity and frequency.
- The implantation procedure is minimally invasive with few side effects and the stimulation therapy is very well tolerated.
- Neurostimulation is a viable option for the management of drug-resistant cluster headache.
- The Pulsante microstimulator system is the first and only implantable system designed specifically for neuromodulation of the sphenopalatine ganglion.
- Preprocedure imaging is critical for evaluation of midface anatomy to determine whether a patient is an appropriate candidate for SPG stimulation.
- The implantation procedure is minimally invasive with few side effects, and the stimulation therapy is very well tolerated.
- Sphenopalatine ganglion stimulation may have a medication-sparing effect for patients suffering from refractory CH.

Cluster headache (CH) is a primary headache disorder. The use of neuromodulation in treatment of CH is well documented. The sphenopalatine ganglion (SPG) has long been a target for management of CH. Intervention at the level of the SPG can interrupt the trigemino-autonomic reflex, which mediates CH pain. The Pulsante system is the only device on the market created for SPG stimulation. The Pulsante device consists of the device body, a lead with six stimulating electrodes placed in the pterygopalatine fossa, and a fixation plate to allow anchoring of the device to the maxilla. Stimulation is administered via a patient-controlled handheld remote control held over the cheek. SPG stimulation is an important treatment option for CH patients.

First draft submitted: 19 October 2018; Accepted for publication: 9 August 2019; Published online: 6 September 2019

Keywords: cluster headache • neuromodulation • Pulsante microstimulator • refractory cluster headache • sphenopalatine ganglion stimulation

Cluster headache (CH) is a primary headache disorder and is considered to be one of the most painful sensations known to man. It is often referred to as the 'suicide headache' given its high correlation with suicidal ideation [1]. The lifetime incidence of CH is estimated at 124 per 100,000 people with a 1-year incidence of 53 per 100,000 people [2], and an annual prevalence of 0.12% [3]. Symptoms consist of severe, unilateral periorbital or temporal facial pain with ipsilateral autonomic features. CH attacks frequently occur with seasonal or circadian rhythmicity and are often accompanied by a feeling of restlessness or agitation. CH attack frequency ranges from eight-times per day to once every other day with each attack lasting 15–180 min. Attacks occur in a relapsing–remitting fashion and, in 15–20% of patients, attacks occur more frequently with remission periods of <4 weeks in a year. This subset is considered to have chronic CH (cCH).

The precise etiology of CH is unknown but genetics may play a role [2,4]. For several years there has been debate on whether CH attacks are caused by a peripheral lesion or a central lesion. Peripheral vasodilation has been

demonstrated in CH attacks, and CH pain can be induced with administration of vasodilators such as alcohol, histamine and nitroglycerin. However, one study showed that CH attacks can still occur even after vasodilation is disrupted and peripheral trigeminal nerve lesioning does not resolve CH pain [2,5]. Further, a peripheral lesion cannot explain the punctual time and seasonal recurrence in CH.

It has been suggested that the causative lesion for CH is located in the hypothalamus and this hypothesis is supported by the temporal and behavioral patterns associated with the disease. Studies of CHs have shown activation of the hypothalamus during both spontaneous and provoked attacks [5]. Although the exact influence of the hypothalamus on CH attacks is unknown, it is felt that the hypothalamus is likely responsible for initiating attacks, and the trigeminal and autonomic nuclei are responsible for initiating and sustaining the pain and autonomic features [5]. This explains the therapeutic rationale for neuronal inhibitors such as lithium, topiramate, divalproex and verapamil for prophylaxis in cCH.

For roughly 1% of cCH patients, CH attacks do not respond to medication management with either neuronal inhibitors or abortive agents such as intranasal zolmitriptan, subcutaneous sumatriptan or high-flow oxygen. For these so-called drug-resistant CH (drCH) sufferers and patients for whom medical therapy is contraindicated, neuromodulation can provide an effective therapeutic option for management of their CH pain.

Neuromodulation in chronic CH

The use of neuromodulation in drCH is well documented. Central neuromodulation in the form of deep brain stimulation (DBS) of the posterior hypothalamus has been used to treat drCH. Studies to date have shown a variable response and morbidity is high. Efficacy is quite varied and studies demonstrate a reduction in CH pain severity ranging from 18 to 87% [6]. The largest randomized controlled trial to date on DBS in cCH demonstrated a $\geq$50% reduction in CH attack intensity in 60% of patients following DBS [7]. However, results from this trial suggest that the treatment effect from DBS is the result of a delayed, neuroplastic process and maximal therapeutic effects may not be perceived for weeks to months [6]. DBS must be considered carefully given the serious adverse events associated with intracranial surgery; there has been a report of lethal hemorrhage following DBS implantation [8].

Peripheral nerve stimulation has also been studied for management of drCH. Occipital nerve and high cervical spinal cord stimulation have both been described. In occipital nerve stimulation (ONS), electrode placement is directed toward the convergence of the upper cervical afferents in the trigemino–cervical complex. Dodick *et al.* [9] wrote one of the first case reports of successful use of ONS for drug-resistant cCH. Overall, ONS has shown favorable results for management of cCH, though benefits may not be evident for several weeks to months similar to DBS [5]. Complications of ONS, however, may limit its utility and include battery replacement, electrode migration, lead breakage and explants due to infection.

Unlike ONS, treatment effects of high cervical spinal cord stimulation can be seen immediately. Wolter *et al.* [10] showed a sustained reduction in cCH attack severity by 39%. However, lead migration is always a concern with cervical leads given the mobility of the cervical spine. Also, high cervical spinal cord stimulation does not mitigate certain risk factors related to ONS, namely battery failures and electrode breakage.

Peripheral vagal nerve stimulation has also been studied for management of CH. The GammaCore™ device was recently approved by the US FDA for this purpose. The ACT2 sham-controlled trial on efficacy of the system was favorable for management of episodic CH but did not show statistically significant improvement of cCH attacks [11].

Sphenopalatine ganglion anatomy

The sphenopalatine ganglion (SPG) has long been a target for management of CH. The SPG is a large extracranial ganglion lying within the pterygopalatine fossa (PPF) in the midface and serves as the final, common pathway for parasympathetic output to the upper face. It contains both sensory and autonomic nerve fibers, and activation of the SPG mimics the autonomic symptoms of CH.

The parasympathetic preganglionic fibers originate in the superior salivary nucleus in the pons before merging with somatic sensory fibers to form the nervus intermedius. The nervus intermedius exits the skull and then joins with motor branches of the facial nerve at the level of the geniculate ganglion prior to exiting the geniculate ganglion as the greater petrosal nerve. Sympathetic fibers traveling to the SPG originate in the upper thoracic spinal cord before synapsing in the cervical sympathetic ganglia. From here postganglionic sympathetic fibers travel to the

pterygoid canal as the deep petrosal nerve where they join with the greater petrosal nerve to form the vidian nerve, or the nerve of the pterygoid canal. Parasympathetic nerve fibers are the only ones to synapse within the SPG.

Efferent nerve fibers from the SPG supply the lacrimal gland, nasal gland, palatine gland and pharyngeal glands via the orbital and maxillary divisions of the trigeminal nerve. This accounts for many of the autonomic features that are seen in CH including conjunctival injection, lacrimation, nasal congestion, rhinorrhea, facial edema, miosis and ptosis. Several postganglionic parasympathetic fibers course superiorly through the SPG into the orbital cavity to innervate meningeal and cerebral vasculature and ultimately promote release of neuropeptides, which are felt to be responsible for the referred head pain.

Activation of the SPG results in release of these neuropeptides and vasoactive substances. This leads to activation of trigeminal sensory fibers causing further activation of the trigeminal pain pathway. This in turn leads to increased parasympathetic outflow. This is known as the trigemino-autonomic reflex. This reflex can initiate and sustain pain, and can create a positive feedback loop of pain and autonomic symptoms in CH [3]. Intervention at the level of the SPG can interrupt this trigemino-autonomic reflex.

SPG stimulation

The first report of SPG blockade for treatment of headaches was published in 1908 [12]. Several decades later Devoghel JC [13] performed what is still the largest study of SPG blockade with intranasal alcohol infiltration for the relief of CH pain; 85% of patients reported pain relief. Despite the reported efficacy of these SPG blockade with local anesthetic, none was able to show sustained relief in cCH. A logical next step was to study the effects of radiofrequency lesioning (RFL) to see whether analgesic efficacy could be prolonged. However, results suggested cCH may be more resistant to RFL than episodic CH [14]. In addition, RFL carries the risk of inadvertent lesioning of adjacent structures [15].

SPG stimulation has emerged as a viable option for treatment of refractory cCH. The first case report of SPG stimulation for drCH was published in 2007 [16]. The initial proof-of-concept study was reported in 2010 [17] and, in the study, 61% of spontaneous or induced CH attacks were completely abolished with SPG stimulation. This study plus several case reports and case series on the efficacy of SPG stimulation for treatment of drug-resistant cCH [18,19] formed the basis for development of the Pulsante® microstimulator implant for SPG neuromodulation. Autonomic Technologies, Inc. (ATI) produced the Pulsante system (also known as the ATI Neurostimulation System) to facilitate SPG neurostimulation implantation within the PPF and it is the only device on the market created for this purpose.

The device consists of the device body, a lead with six stimulating electrodes and a fixation plate to allow anchoring of the device to the maxilla (Figure 1). The implant is positioned such that the stimulating electrodes are placed within the PPF proximate to the SPG nerve bundle on the side of the patient's CH attacks. Stimulation is administered via a patient-controlled handheld remote control held over the cheek (Figure 2). Typically, stimulation parameters are adjusted after stimulator implantation and can be titrated within a preset range by patients during an acute CH attack.

Schoenen *et al.* [8] published the Pathway CH-1 study, the first sham-controlled study of SPG stimulation with the Pulsante device in patients with medication refractory cCH. The primary end point of the study was analgesia after 15 min of stimulation. 64% of the patients in this study were acute responders. Interestingly, 43% of patients experienced a CH attack frequency reduction of ≥50%. In addition, there was a statistically significant reduction in headache disability. The Pulsante system has achieved the CE mark in Europe and the investigational drug exemption in the USA. The second randomized-controlled trial, Pathway CH-2, on use of the Pulsante system is currently ongoing at several sites in the USA [20]. Preliminary results from this study show similar results – 63% of patients experienced pain relief at 15 min following SPG stimulation and 57% maintained this analgesic effect at 60 min [21]. The Pathway CH-2 study shows a similar, statistically significant reduction in frequency of CH episodes as well as a reduction in abortive medication use in patients using SPG stimulation.

The one study on the longitudinal effects of the Pulsante microstimulator for treatment of cCH [22] found that these therapeutic effects persist. At 24 months, 61% of patients achieved a therapeutic response to SPG stimulation for at least half of their CH attacks and 35% of patients reduced the frequency of their CH attacks by over 50%. Overall, 69% of patients reported that the SPG stimulation was useful in the treatment of their headaches at the 24-month follow-up.

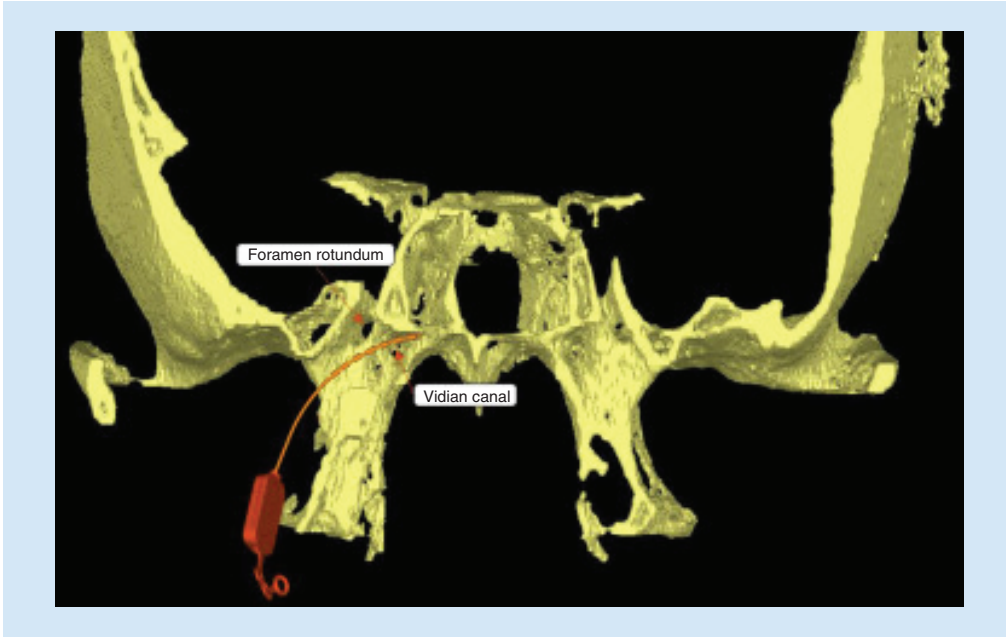


Figure 1. The 3D computed tomography model showing placement of stimulator lead into the pterygopalatine fossa.
Reproduced with permission from [3].

Preoperative planning

Appropriate patient selection is the first step in surgical planning. SPG stimulation is reserved for patients with cCH who have failed medication management or patients in whom use of preventive and acute therapies are contraindicated. Implantation of the Pulsante microstimulation device requires complex knowledge of the relevant anatomy of the midface. Implantation should be avoided in patients who have recently undergone facial surgery near the ipsilateral PPF or received radiation to the area within the preceding 6 months [3]. Similarly, patients with untreated malignancy, active infection or space-occupying lesion that distorts the mid-facial anatomy should be considered very carefully. Preoperative imaging with conventional computed tomography (CT) or cone beam CT can help define the anatomy and determine accessibility of the PPF. The PPF has an inverted triangular shape and, in rare instances, may be fused to the maxillary sinus. The pterygomaxillary fossa opens into the PPF and must be wider than 1 mm in order to accommodate the microstimulator lead, which is 1 mm in diameter.

The Pulsante device is inserted via a transoral gingival incision and, following careful dissection along the maxillary bone, advanced into the PPF. Any patient with a regional infection such as sinusitis or periodontal disease should be treated prior to proceeding with implantation. Similarly, caution should be taken in any patient with significant osteoporosis, maxillary atrophy or previous skull base surgery to avoid malposition, migration or erosion of implant into adjacent structures. Preoperative dental panorex films should be ordered to determine maxillary bone density and identify any dental pathology in the maxillary molars and premolars.

Preoperative imaging can also help with stimulator selection. The Pulsante microstimulator comes in four sizes: short (3.6 mm), medium (4.4 cm), long (5.2 cm) or extra long (6.0 cm). The appropriate size is determined by measuring the distance from the sphenopalatine foramen to the posterolateral maxilla medial to the zygomatic bone. In Assaf *et al.* [3] study, this distance was determined using a 3D recreation of the preoperative CT scan using Mimic 3D software.

Intraoperative imaging is also crucial for correct Pulsante placement. Fluoroscopy is used to visualize advancement of the microstimulator into the PPF. VolView software can be used to create a digitally reconstructed 2D representation of the 3D rendering to allow for direct comparison with fluoroscopy images taken during implantation. Once positioned, the microstimulator is anchored to the maxilla. Placement can be confirmed with an intraoperative CT or 3D cone beam CT. If this is not available, a CT scan should be performed on the first postoperative and, if repositioning is required, it should be done as soon as possible after initial placement [3].

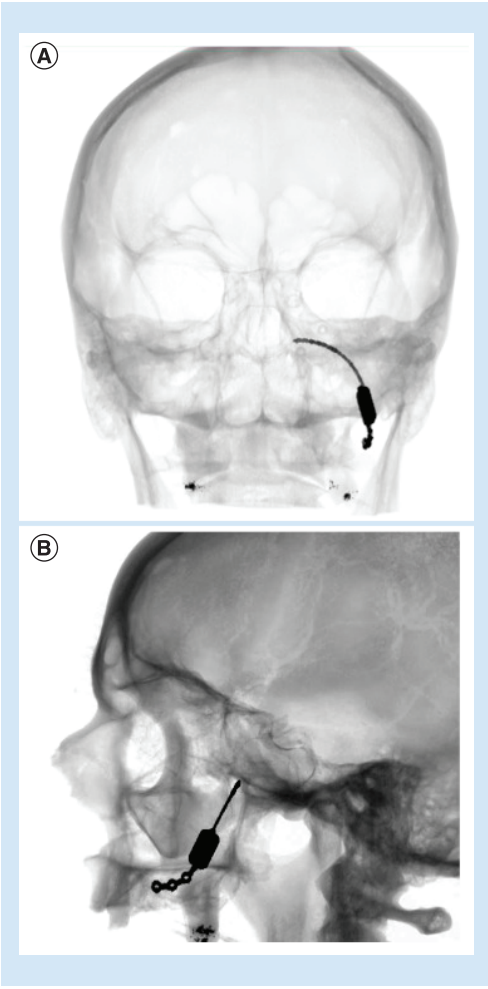


Figure 2. Radiographs showing final placement location of stimulator. (A) Anterior–posterior radiograph and **(B)** lateral radiograph showing placement of sphenopalatine ganglion stimulator.
Reproduced with permission from [3].

Stimulation parameters

The initial weeks following Pulsante placement should be reserved for titration of stimulation. The patient should ideally be seen every 2 weeks as needed for adjustment [8,18] and maximum amplitude should be set to slightly higher than that, which provoked discomfort [23]. Stimulation parameters are individual to the patient, but several studies have shown that high-frequency stimulation is preferred over lower frequencies. In fact, low-frequency stimulation has been shown to induce CH attacks [24] and, though frequencies up to 60 Hz are able to activate the parasympathetic arm of the trigemino-autonomic reflex, effects are transient [8]. In the Pathway-1 study, the mean stimulation frequency was 120.4 ± 15.5 Hz. It is unclear why high frequency stimulation achieves better efficacy but it is postulated that HF stimulation causes depletion of stored neuropeptides over time [8].

The stimulation for a well-positioned implant should be perceived as a paresthesia at the root of the nose. Paresthesia sensed in the upper teeth and gums or hard palate signifies stimulation of the maxillary nerve and greater and lesser palatine nerves, respectively.

Benefits

There are many benefits to the Pulsante microstimulator system. In a large subset of patients, SPG stimulation is effective as a monotherapy obviating the need for expensive medications. Use of the Pulsante microstimulator can lead to reduced medication costs and may provide a cost saving after several years of use [25]. The Pulsante microstimulator implantation is a destination therapy and, as there is no internal battery, battery fade is not a consideration. Unlike ablative procedures, implantable SPG stimulation is reversible and does not cause any damage to neural tissues. Not only it is effective for management of acute CH attacks, several studies have shown use of Pulsante microstimulator leads to reduced CH attack frequency [8,18,25–27]. The patient-controlled remote

control allows for easily accessible, on-demand, targeted therapy to be delivered immediately at the onset of a CH attack.

Drawbacks

The SPG stimulator requires a minimally invasive surgery for implantation. The most common side effects of this surgery are sensory disturbances (most commonly numbness along the distribution of the maxillary nerve), facial pain and swelling. Most cases were mild and resolved gradually over 3 months [3,28]. SPG stimulation has not been studied for use in children and pregnant or lactating women. The phenomenon of side shift has been described for most types of neuromodulation for CH. The concept describes that attacks may shift to the side contralateral to the implant, which is one negative side effect of the treatment. There has been only one case report of simultaneous, bilateral SPG stimulator implantation in a patient with side-alternating attacks [28] but this may prove to be a viable option in the future.

Conclusion

CH is a very severe form of facial pain associated with high disability. The Pulsante microstimulator provides a minimally invasive option for patients suffering from drug-resistant CHs. Patients have a titratable stimulator system that has a dual action: amelioration of CH attacks and reduced attack frequency. The side effects to the procedure are typically mild and resolve over time. Eighty percent of patients who completed the Pathway CH-1 study stated they would make the same decision again.

Financial & competing interests disclosure

No direct funding was used for this project. The authors are employees of the Duke University Health System. L Roy serves as a consultant for Medtronic, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest

1. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache* 52(1), 99–113 (2012).
2. Leone M, Bussone G. Pathophysiology of trigeminal autonomic cephalalgias. *Lancet Neurol.* 8(8), 755–764 (2009).
3. Assaf AT, Hillerup S, Rostgaard J *et al.* Technical and surgical aspects of the sphenopalatine ganglion (SPG) microstimulator insertion procedure. *Int. J. Oral Maxillofac. Surg.* 45(2), 245–254 (2016).
   - **Excellent review of all aspects of the surgical technique for sphenopalatine ganglion (SPG) stimulator implantation including presurgical evaluation and postoperative considerations.**
4. Ekbom K, Hardebo JE. Cluster headache: aetiology, diagnosis and management. *Drugs* 62(1), 61–69 (2002).
5. Lainez MJ, Guillamon E. Cluster headache and other TACs: pathophysiology and neurostimulation options. *Headache* 57(2), 327–335 (2017).
6. Vyas DB, Ho AL, Dadey DY *et al.* Deep brain stimulation for chronic cluster headache: a review. *Neuromodulation* doi:10.1111/ner.12869 (2018) (Epub ahead of print).
7. Fontaine D, Lazorthes Y, Mertens P *et al.* Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. *J. Headache Pain* 11(1), 23–31 (2010).
8. Schoenen J, Jensen RH, Lanteri-Minet M *et al.* Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. *Cephalalgia* 33(10), 816–830 (2013).
   - **Results of the first randomized-controlled trial of SPG stimulator implantation for management of chronic, refractory cluster headache.**
9. Dodick D, Trentman T, Zimmerman RS, Eross EJ. Occipital nerve stimulation for intractable chronic primary headache disorders. *Cephalalgia* 23, 701–701 (2003).
10. Wolter T, Kiemen A, Kaube H. High cervical spinal cord stimulation for chronic cluster headache. *Cephalalgia* 31(11), 1170–1180 (2011).
11. Goadsby PJ, De Coo IF, Silver N *et al.* Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a randomized, double-blind, sham-controlled ACT2 study. *Cephalalgia* 38(5), 959–969 (2018).

12. Sluder G. The role of the sphenopalatine ganglion in nasal headaches. *NY State J. Med.* 27, 8–13 (1908).
- **First published report of SPG block for trigeminal autonomic cephalalgia.**

13. Devoghel JC. Cluster headache and sphenopalatine block. *Acta Anaesthesiol. Belg.* 32(1), 101–107 (1981).

14. Mojica J, Mo B, Ng A. Sphenopalatine ganglion block in the management of chronic headaches. *Curr. Pain Headache Rep.* 21(6), 27 (2017).

15. Sanders M, Zuurmond WW. Efficacy of sphenopalatine ganglion blockade in 66 patients suffering from cluster headache: a 12- to 70-month follow-up evaluation. *J. Neurosurg.* 87(6), 876–880 (1997).

16. Ibarra E. Neuromodulacion del ganglio esfenopalatino para aliviar los sintomas de la cefalea en racimos. Reporte de un caso. *Headache* 347, 951–962 (2007).

17. Ansarinia M, Rezai A, Tepper SJ *et al.* Electrical stimulation of sphenopalatine ganglion for acute treatment of cluster headaches. *Headache* 50(7), 1164–1174 (2010).

18. Lainez MJ, Marti AS. Sphenopalatine ganglion stimulation in cluster headache and other types of headache. *Cephalalgia* 36(12), 1149–1155 (2016).

19. Barloese M, Petersen A, Stude P, Jurgens T, Jensen RH, May A. Sphenopalatine ganglion stimulation for cluster headache, results from a large, open-label European registry. *J. Headache Pain* 19(1), 6 (2018).
- **Open label trial of SPG stimulation in chronic, refractory cluster headache sufferers, which also attempted to define prophylactic effect of Pulsante® system.**

20. Autonomic Technologies, Inc. Sphenopalatine ganglion stimulation for the treatment of chronic cluster headache (2019). https://clinicaltrials.gov/ct2/show/NCT02168764?term=autonomic+technologies

21. Sharan A. Sphenopalatine ganglion stimulation. Presented at: *North American Neuromodulation Society 22nd Annual Meeting.* Las Vegas, NV, USA (17–20 January 2019).

22. Jurgens TP, Barloese M, May A *et al.* Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. *Cephalalgia* 37(5), 423–434 (2017).
- **Extension of the Pathway CH-1 study showing long-term efficacy of SPG stimulation.**

23. Martelletti P, Jensen RH, Antal A *et al.* Neuromodulation of chronic headaches: position statement from the European Headache Federation. *J. Headache Pain* 14, 86 (2013).

24. Schytz HW, Barlose M, Guo S *et al.* Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. *Cephalalgia* 33(10), 831–841 (2013).

25. Pietzsch JB, Weber SA, Lund N, Gaul C. Changes in medication cost observed in chronic cluster headache patients treated with sphenopalatine ganglion (SPG) stimulation: analysis based on 1-year data from the Pathway R-1 Registry. *Cephalalgia* 38(8), 1455–1462 (2018).
- **Sought to find the economic impact of SPG stimulation for refractory cluster headache.**

26. Fontaine D, Santucci S, Lanteri-Minet M. Managing cluster headache with sphenopalatine ganglion stimulation: a review. *J. Pain Res.* 11, 375–381 (2018).

27. Magis D, Schoenen J. Advances and challenges in neurostimulation for headaches. *Lancet Neurol.* 11(8), 708–719 (2012).

28. Meng DW, Zhang JG, Zheng Z, Wang X, Luo F, Zhang K. Chronic bilateral sphenopalatine ganglion stimulation for intractable bilateral chronic cluster headache: a case report. *Pain Physician* 19(4), E637–E642 (2016).