Chapter 13
Neurostimulation: Why, When, and Which One?

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Neuromodulation has been proposed for more than a decade to treat primary headaches including cluster headache. Neuromodulation can be separated into invasive techniques, that is, with a surgical procedure to implant the stimulation device, and noninvasive techniques (transcutaneous or transcranial stimulation). For the treatment of cluster headache (CH), the only noninvasive neuromodulation technique studied up to now is vagus nerve stimulation (cervical portion), while invasive neuromodulation has been applied to target the posteroinferior hypothalamic area, the great occipital nerve, or the sphenopalatine ganglion. For each target, we will review key elements in terms of background, efficacy evidence, limits, and mechanisms of action.

13.1 Vagus Nerve Stimulation

13.1.1 Background

Vagus nerve stimulation has been considered as a promising treatment of primary headaches following migraine improvement in epileptic patients with a migraine comorbidity, while their epilepsy was treated by implanted vagus nerve stimulation [1]. Recent devices allowing a noninvasive stimulation of the vagus nerve (nVNS)

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have increased interest for this target, the gammaCore® device having been meanwhile specifically developed for the treatment of headache by noninvasive stimulation of the cervical branch of the vagus nerve.

13.1.2 Evidence

PREVA study is an *open* randomized controlled trial (RCT) in which nVNS was examined as adjunctive prophylactic treatment of chronic CH [2]. The PREVA study compared adjunctive prophylactic nVNS (n = 48) with standard of care (SoC), i.e., medications alone as a control (n = 49). A 2-week baseline phase was followed by a 4-week randomized phase (SoC plus nVNS vs. SoC alone) and a 4-week extension phase (SoC plus nVNS). The primary endpoint was the reduction in the mean number of CH attacks per week. During the randomized phase, individuals in intent-to-treat population treated with SoC plus nVNS (n = 45) had a significantly greater reduction in the number of attacks per week compared to those receiving SoC alone (n = 48) (−5.9 vs. −2.1, respectively) for a mean therapeutic gain of 3.9 fewer attacks per week (95% CI: 0.5–7.2; p = 0.02). This preventive effect was maintained during the 4-week extension phase during which all patients benefited from nVNS [3]. Using PREVA study data, a pharmacoeconomic model from the German statutory health insurance perspective showed cost-effectiveness of nVNS, suggesting that adjunctive nVNS provides economic benefits in the treatment of chronic CH [4].

The PREVA study did not show any evidence of nVNS efficacy for the acute treatment of CH in patients with chronic CH [5]. Conversely, nVNS showed its efficacy to abort or relieve attacks of episodic CH in two large sham-controlled trials (ACT1 and ACT2, ref.). ACT2 study is a RCT that compared nVNS with a sham (placebo) device for acute treatment in patients suffering from episodic or chronic CH [6]. After completing a 1-week run-in period, subjects were randomly assigned to receive nVNS or sham stimulation during a 2-week double-blind period. The primary efficacy endpoint was the proportion of all treated attacks that achieved pain-free status within 15 min after treatment initiation, without rescue medication. The Full Analysis Set comprised 48 nVNS-treated (14 episodic CH, 34 chronic CH) and 44 sham-treated patients (13 episodic CH, 31 chronic CH). From the primary endpoint, nVNS (14%) and sham (12%) treatments were not significantly different for the entire CH population. No significant differences were seen between nVNS (5%) and sham (13%) in the chronic CH subgroup. By contrast, nVNS (48%) was superior to sham (6%; $p < 0.01$) in the episodic CH subgroup. Efficacy of nVNS for the acute treatment of episodic CH was also supported by the ACT1 study [7]. ACT1 study is a RCT similar to ACT2, but the primary endpoint was the response rate, defined as the proportion of subjects who achieved pain relief at 15 min after treatment initiation for the first attack without any rescue medication use through 60 min. The intent-to-treat population comprised 133 subjects: 60 nVNS-treated (episodic CH, n = 38;

chronic CH, n = 22) and 73 sham-treated (episodic CH, n = 47; chronic CH, n = 26). Again, response rates were overall not significantly different between nVNS-treated and sham-treated patients (26.7% vs. 15.1% p = 0.1), but were significantly higher with nVNS than with sham when the episodic CH subgroup was considered (34.2% vs. 10.6%; p = 0.008).

13.1.3 Limits

Evidence supports the use of nVNS as an acute treatment of episodic CH and as a prophylactic treatment of chronic CH. Nevertheless, based on clinical experience, therapeutic benefit from prophylactic treatment would be more convincing than from acute treatment especially in chronic CH [8]. Acute nVNS use requires the self-application of three stimulation sessions of 2 min each separated by 1 min from the beginning of the attack. For preventive use, the administration of a stimulation period of 2 min three times a day is necessary and must be evaluated over 3 months. The gammaCore® device has only one nVNS program. The subject can use the device on the right or left sides of the neck by putting it next to his/her carotid pulse (usually alternate sessions are recommended). Intensity is raised until the subject feels a tingling sensation deep in the neck, and the device is well positioned when the subject feels a tightness of its lower lip (due to platysma muscle contraction). Safety and tolerability of nVNS with gammaCore® was confirmed by the three RCTs (PREVA, ACT1, ACT2) performed in CH. In these trials, the side effects (voice change, skin irritation, muscle contraction, dysesthesia) were mild to moderate and all transient [2, 6, 7]. The manufacturer of gammaCore® advises not to use it in pregnancy and in the following situations: cervical atheroma, implanted stimulator, high blood pressure, hypotension, tachycardia, bradycardia, cervical vagotomy, and metallic device implanted in the cephalic segment. This device has a CE mark, but it is not reimbursed by all health insurance systems. It is available, on prescription, on the manufacturer's website (https://gammacore.com) at a rate of 260 €. Although comparable to the triptan budget, this price might therefore represent a limit to nVNS use, especially as this device allows a limited number of stimulations (or "doses," up to 300) but its battery cannot be recharged. Thus, a new device must be purchased at the end of the battery.

13.1.4 Mechanism of Action

The precise mechanism of action of nVNS in primary headaches is not known, but corpus of data is available and allows certain assumptions [9]. The reality of vagus nerve stimulation by gammaCore® has been confirmed using a neurophysiological approach in healthy volunteers, which showed that cervical nVNS induced evoked

nerve potentials similar to those induced by invasive vagus nerve stimulation devices [10]. Similarly, a functional magnetic resonance imaging study, also performed in healthy controls stimulated by gammaCore®, highlighted an activation of the solitary tract nucleus, which is the main central relay of vagal afferences [11]. The therapeutic effect of nVNS is probably mediated by the stimulation of large myelinated fibers as argued by magnetic resonance-based model predicting the properties of the induced electric field in different anatomical planes [12]. The lack of C fibers recruitment suggested by this model accounts for the absence of pain and parasympathetic signs with nVNS using gammaCore®. Experimental works have also tried to specify the mechanism of the therapeutic effect of gammaCore® in primary headaches. Centered on migraine, a first experimental work has shown an inhibition of cortical spreading depression (CSD) support of the migraine aura and possible trigger of migraine headache [13]. Another study, focused on trigeminal pain and performed on a murine model of trigeminal allodynia induced by dural inflammation, has shown a significant reduction in periorbital skin sensitivity for more than 3.5 h after nVNS, this reduction being associated with a reduction of extracellular glutamate concentration in the trigemino-cervical complex [14]. A neuroimaging study showed an activation of the solitary tract nucleus that was associated to changes in the pain matrix (parabrachial nucleus, primary somatosensory cortex, and the insula) and the trigemino-cervical complex [11]. Finally, an experimental electrophysiological work demonstrated the ability of implanted vagus nerve stimulation to reduce dose-dependent nociceptive activation of neurons of the trigemino-cervical complex and the superior salivary nucleus which are the two essential relays of the trigemino-autonomic pathway supporting primary headaches like migraine and cluster headache [15].

13.2 Deep Brain Stimulation of Posteroinferior Hypothalamic Area

13.2.1 Background

Deep brain stimulation (DBS) of the posteroinferior hypothalamus has been the first neuromodulation technique to be proposed in drug-refractory chronic CH. The initial concept was to inhibit the presumed CH attack generator [16, 17] identified in this area shortly before, by neuroimaging studies. Indeed, positron emission tomography (PET) imaging during CH attacks showed a specific activation of an area located at the diencephalo-mesencephalic region, close to the floor of the third ventricle [18]. Based on its projection on the Talairach grid, this region has been called posteroinferior hypothalamus.

13.2.2 Evidence

Preventive treatment with high-frequency (130 Hz) DBS of the posteroinferior hypothalamus area has been reported in the literature in about 80 patients up to now (Table 13.1) [16, 17, 19–27] with an overall 50% responders' rate (≥50% decrease of attack frequency) of 62.8%, including 30% of patients being almost pain-free at longer follow-up. This approach has been evaluated in controlled conditions by a single study [22]. However due to methodological issues, including the too short duration (1 month) of the randomized periods, this RCT failed to demonstrate a significant decrease of CH attacks with DBS (ON) compared to control (OFF) conditions. As a matter of fact, retro-hypothalamic DBS therapeutic effect may be delayed, and a clinically significant headache decrease can be observed in an interval ranging from 1 to 86 days. Several studies reported that some patients with a long follow-up showed few bouts of attacks per year, like episodic CH.

13.2.3 Limits

DBS is the last-line preventive treatment of the most severe chronic CH patients and should only be practiced by medico-surgical teams combining headache expertise and functional neurosurgery expertise with a strict respect of patient selection criteria (at least 2 years of disease duration, at least one attack per day, resistance to pharmacotherapy including verapamil and lithium, headache "locked" to the same side, normal neurological examination, and absence of psychiatric comorbidity) [28, 29]. This position as a last-line treatment is justified by the invasiveness and the

Table 13.1 Open series and RCT related to DBS in chronic CH

Study	Patients (*n*)	Country	Mono/ multi centric	Mean follow-up (years)	At least 50% improvement (*n*)
Leone et al. [17, 23], and Franzini et al. [16]	17	Italy	Mono	8.7	12
Schoenen et al. [25]	6	Belgium	Mono	4	3
Starr et al. [27]	4	USA	Mono	1	2
Owen et al. [24]	1	GB	Mono	0.7	1
Bartsch et al. [20]	6	Germany	Mono	1.4	3
Fontaine et al. [22] (RCT)	11	France	Multi	1	6
Seijo et al. [26]	5	Spain	Mono	2.8	5
Akram et al. [19]	21	GB	Mono	1.5	11
Chabardès et al. [21]	7	France	Mono	1	6
Total	78				49 (62.8%)

risks of this therapeutic approach. If few side effects are related to the stimulation itself (essentially gaze disturbances), the implantation of the electrode can be associated to brain hemorrhages which can be fatal [25]. This risk can be reduced by endoventricular stimulation of the hypothalamus using a floating DBS electrode laid on the floor of the third ventricle [21].

13.2.4 Mechanisms of Action

The common target used for posteroinferior hypothalamic DBS is located 5 mm below the mid-commissural point (MCP), 2 mm lateral to the midline, and 3 mm posterior to the MCP [16], although stimulation delivered from an electrode located on the floor of the third ventricle is also effective [21]. The neural structure corresponding to these coordinates and whose stimulation induces the therapeutic effect is still debated. Fontaine and colleagues studied the anatomical locations of the DBS electrodes and identified several candidates [30], including the mesencephalic gray substance, the ventral tegmental area, and several tracts connecting the hypothalamus with autonomic nuclei of the brain stem. Recently, a more precise modeling of volume of cerebral tissue activated by DBS in responders and non-responders was used to identify the region associated with the highest improvement [19]. The spot that correlated with better outcome was located 6 mm lateral, 2 mm posterior, and 1 mm inferior to MCP, in an area between the red nucleus and the mammillothalamic tract, encompassing the ventral tegmental area and mesencephalic gray and the lateral wall of the floor of the third ventricle (explaining the efficacy of DBS lead implanted in the V3). An additional tractography study showed that this area was crossed by a so-called trigemino-hypothalamic tract, connecting the trigeminal system (and other brain stem nuclei associated with nociception and pain modulation) with the hypothalamus, the prefrontal, and the mesio-temporal area. However, as the electrodes' coordinates are usually similar in DBS responders and non-responders, failure of DBS in CH may be caused by factors other than electrode misplacement, likely related to the disease itself.

Very few neuroimaging studies have explored brain activity changes following retro-hypothalamic DBS. May et al. studied the acute (60 s) effects of DBS by positron emission tomography. They reported cerebral blood flow changes induced by stimulation in the ipsilateral posterior hypothalamic gray (site of electrode implantation), the ipsilateral thalamus, the somatosensory cortex and precuneus, the anterior cingulate cortex, and the ipsilateral trigeminal nucleus and ganglion [31]. A magnetoencephalography study in a single patient reported short-term (10 min) retro-hypothalamic DBS-induced activity changes in the orbitofrontal cortices and in the periaqueductal gray [32]. No study explored long-term effect of DBS in chronic CH patients. Together, these data suggest two alleged mechanisms of action for DBS in CCH. First is the inhibition of a CH generator located in the hypothalamus via stimulation of afferent fibers located in the retro-hypothalamic area. This mechanism might be specific to CH. Second is the modulation of non-

specific antinociceptive systems, including the mesencephalic gray substance, and the orexinergic system [33] leading to modulation of regions belonging to the "pain matrix."

13.3 Occipital Nerve Stimulation

13.3.1 Background

Occipital nerve stimulation (ONS) is characterized by the application of a continuous electrical stimulation over the great and/or lesser occipital nerves (respectively, GON and LON), using a subcutaneous chronically implanted electrode that is placed close to the nerve and connected to a battery. This procedure was originally described by Weiner and Reed [34] and has been first proposed to treat occipital neuralgia and then primary headaches, including CH.

13.3.2 Evidence

The demonstration of ONS efficacy in controlled conditions is challenging because its clinical effect is conditioned by the induction of paresthesia within the GON territory, which limits the double-blind. The ICON study was set up with a methodology aiming to maintain as much as possible this double-blind [35]. This RCT, comparing high-amplitude (100%) and low-amplitude (30%) ONS, is ongoing (NCT01151631, as for March 2018), and, pending its results, the use of ONS in the preventive treatment of chronic CH is only supported by data obtained under uncontrolled conditions [26, 36–46] (Table 13.2).

ONS was first experimented by Schwedt and colleagues with beneficial effect on headache frequency, duration, and intensity in one patient with refractory chronic CH [47]. Subsequently, Magis and colleagues suggested the interest of ONS in the preventive treatment of refractory chronic CH by reporting an attack frequency reduction of more than 50% in five out of eight subjects treated in a prospective pilot study [42]. These results were duplicated by Burns and colleagues who reported a similar percentage of responders in another open pilot study including eight patients [36]. These two teams confirmed their preliminary results in larger longer-term trials [37, 43], and other European centers proposed ONS in a compassionate use to patients with refractory chronic CH and reported results in larger series. Thus, Leone and colleagues reported a 50% attack frequency reduction in 20 (66.7%) out of 35 patients with a median follow-up of more than 6 years [41]. A lower (46.1%) 50% responders' rate was reported by Miller and colleagues, but 19 of the 51 included patients presented another primary headache associated with their chronic CH. Considering the subpopulation of patients with chronic CH alone, the 50% responders' rate was 53.1% [44]. In a prospective multicenter series including

Table 13.2 Open series related to ONS in chronic CH

Study	Patients (*n*)	Country	Mono/ multi centric	Mean follow-up (months)	At least 50% improvement (*n*)
Magis et al. [42, 43, 53]	15	Belgium	Mono	36.8	12
Burns et al. [36, 37]	14	GB	Mono	17.5	5
de Quintana-Schmidt et al. [38]	4	Spain	Mono	6	4
Mueller et al. [46]	24	Germany	Mono	20	21
Fontaine et al. [39]	13	France	Multi	14.6	10
Strand et al. [61]	3	USA	Mono	10	2
Fontaine et al. [40]	44[a]	France	Multi	12	26
Miller et al. [44]	32[b]	GB	Mono	42.6	17
Leone et al. [41]	35	Italy	Mono	73.2	20
Total	184				117 (63.6%)

[a]Only patients with complete after 12 months follow-up
[b]Only patients with CH alone

44 chronic CH sufferers treated by ONS with 1-year follow-up, the French ONS registry has reported a 30% attack frequency reduction and a 50% attack frequency reduction in 28 (64%) and 26 (59%) of patients, respectively, whereas near half of patients were considered as excellent responders according to a composite criterion associating a 30% attack frequency reduction, a high level of satisfaction, and a stability or a reduction in preventive pharmacological treatment [40].

Overall, ONS procedure presents a 66% success rate (improvement >50%) (Table 13.2). An obvious limitation is the lack of controlled conditions. This is of particular concern as a significant placebo effect is seen in CH like in other primary headaches; and the natural history of CH is often characterized by fluctuations and spontaneous remissions. Nevertheless, two main elements in collected data suggest more than a placebo effect or a natural history: the preceding very long duration of the chronic phase in the implanted patients and the rapid worsening and recovery after technical failures which appears as consistent finding across the series.

Beyond the preventive effect of ONS, analysis of the collected data provided important additional informations for the clinical practice. Some patients found that ONS helped abort acute attacks but acute use of ONS is not supported by the literature. Similarly, the available data do not suggest that ONS reduces the duration and the intensity of CH attacks. Retrospective evaluation of time to improvement in individual cases appears to show two groups, the first being patients with quick improvement in few weeks and the second being those gradually improving over months. Burns and colleagues stated that the group with delayed improvement has a lesser ONS benefit than the group with quick improvement [37] but such a difference in benefit was not confirmed later.

13.3.3 Limits

The European Headache Federation considers ONS as a valuable therapeutic alternative in drug-refractory chronic CH [29] with a statement supported by evidence and the benefit/risk ratio of this approach sometimes considered as "minimally invasive." Nevertheless, ONS is not devoid of side effects. As any invasive neuromodulation technique, ONS exposes to a risk of immediate or delayed infections. On the other hand, ONS is associated with two adverse events of its own. The first one is a fast battery depletion (mean life from 1 to 2 years) due to high current consumption related to high intensity and duration (daytime and nighttime) of the stimulation. This depletion requires battery replacement in up to 100% of patients at long term and increases the cost of this treatment, especially in countries where rechargeable batteries are not allowed in first-line use. The second adverse event limiting ONS is the lead migration due to neck movements. Migration, like the other complications concerning leads (fracture, skin erosion), is partly related to surgical implantation technique. Multiple surgical techniques have been reported in the literature, using percutaneous cylindrical or surgical paddle leads, approach from the midline or from retro-mastoid incision(s) [48], but no evidence is available claiming the superiority of one technique over others in terms of complication incidence. One of the main important technical aspects to limit the risk of migration is a firm anchorage of the lead. This point has been considered by manufacturers, and, in order to limit the risk of migration, Medtronic has developed a new electrode specifically dedicated to the ONS (Ankerstim®), which has just obtained its CE marking but will need to demonstrate its superiority in CH therapy.

Bilateral stimulation is recommended to treat CH to avoid headache side-shift, which has been reported in up to one third of the patients stimulated unilaterally [36, 37]. Trial stimulation is not useful because some patients can improve after several months of continuous stimulation [39]. Response to occipital nerve block is not useful in selecting patient for ONS treatment [49], but a recent retrospective study showed that prior response to greater occipital nerve block was associated with increased likelihood of ONS response [5].

13.3.4 Mechanisms of Action

If several hypotheses have been proposed to understand how ONS improves CH patients, its exact mechanism of action remains unknown. ONS could act through the modulation of the convergent nociceptive inputs in the trigemino-cervical complex [50, 51], by a "gate control theory-like" mechanism [52]. Nevertheless, the latency of the effect appearance in many patients with CH benefiting from ONS makes one consider a more complex mechanism. This mechanism would be generic and imply structures involved in pain modulation. Two arguments suggest that ONS might act through a non-specific regulation of the central pain control systems

rather than modulation of a central CH generator. Firstly, some successfully ONS-treated chronic CH patients still report autonomic attacks without pain [36, 37, 47]. Secondly, a functional imaging study has described ONS-induced metabolic changes in the "pain matrix," especially in the perigenual anterior cingulate cortex in ONS responders, but no change in the ipsilateral hypothalamic [53]. These results should be duplicated to confirm the absence of hypothalamic change in ONS responders and the symptomatic character of this treatment. MET-ONS study, a similar functional imaging study performed by the French ONS registry, included 18 patients with chronic CH treated with ONS, and its results are being analyzed (NCT02081482/clinicaltrials.gov).

13.4 Stimulation of the Sphenopalatine Ganglion

13.4.1 Background

The sphenopalatine ganglion has been chosen as a valuable target of neuromodulation due to the involvement of the parasympathetic system in the pathophysiology of trigeminal autonomic cephalalgias. This background justified a proof-of-concept study with five patients with CH in which the majority of attacks could be controlled by a sphenopalatine ganglion stimulation (SPGS) via an electrode connected to an external stimulator [54]. This neuromodulation approach could be considered in a practical perspective through the development of Pulsante® (Autonomic Technologies, USA) which is an original implantable SPG microstimulator allowing to abort CH attacks on demand. Specifically designed for acute SPGS, the device is implanted along the posterior wall of the maxillary bone in the pterygopalatine fossa (PPF), fixed with a screwed plate to the zygomatic process, and the lead is in contact with the sphenopalatine ganglion. No battery is contained in the neurostimulator, so power and activation are initiated transcutaneously by a remote controller using radio-frequency energy.

13.4.2 Evidence

Evidence supporting SPGS by Pulsante® is limited to CH with the PATHWAY CH-1 study which is a RCT promoted by ATI to evaluate this device in the treatment of cluster headache attacks [55]. This multicenter randomized sham-controlled study tested the safety and efficacy of the Pulsante® device. Thirty-two patients suffering from refractory chronic CH were enrolled and 28 completed the randomized experimental period. Optimal, suboptimal, or sham stimulation were randomly used to treat each CH attack, and pain relief 15 min after the start of the SPGS was the main criterion. Pain relief was achieved in 67.1% of optimal stimulation-treated attacks compared to 7.4% of sham-treated and 7.3% of suboptimal-treated attacks ($p < 0.0001$). Absence of pain was achieved in 34.1% and 1.5% of attacks after

optimal stimulation and sham stimulation, respectively ($p < 0.0001$). Nineteen of 28 (68%) patients experienced a clinically significant improvement, but only 32% achieved a pain relief in more than 50% of the treated attacks.

Results of the long-term (24 months) open extension phase of PATHWAY CH-1 study have been recently published [56]. This open extension phase involved 33 patients who were initially included in the PATHWAY CH-1 study, although 11 of them were not included in the first analysis for time reasons. Moreover, ten patients included in the initial study were excluded from this long-term analysis, because they no longer had the stimulator implanted or due to previous protocol noncompliance. Across all 33 patients, a total of 5956 attacks were treated. Effective treatment (pain relief and/or absence of pain) was achieved in 65% of CH attacks, with a delay of 11.2 min on average, including 50% becoming pain-free. Fifteen out of 33 patients (45%) were considered as acute responders (at least 50% of attacks were successfully treated). In 79% of the attacks, patients did not report the use of acute medication.

In PATHWAY CH-1 study, there was also an unexpected reduction in attack frequency noted with repetitive attack stimulation in 12 of 28 (43%) patients who experienced a reduction in attack frequency of at least 50% (average 88%). This reduction was confirmed in the open extension phase and suggested that repeated use of SPG stimulation might act as a CH preventive treatment. Nevertheless, this study was not designed to demonstrate a preventive effect, and spontaneous transformation from chronic to episodic forms of the disease cannot be excluded.

13.4.3 Limits

According to available evidence, SPGS with Pulsante® should be dedicated to the acute treatment of chronic CH. This device is indicated for patients with strictly lateralized attacks and, intuitively, mostly indicated in those with no response to oxygen inhalation and subcutaneous sumatriptan administration and those with a high daily number of attacks since the system allows a 5-min stimulation that can be repeated as many times as needed. The place of SPGS is also to be determined in patients who suffer from an episodic CH form with painful bouts of long duration and the same attack characteristics. Finally, implanted patients with Pulsante® will likely try to use this device as a preventive treatment by administering one or two stimulations of 15 min per day outside their attacks [57]. Immediately after implantation, use of Pulsante® requires a learning phase to allow patients to find the stimulation parameters producing paresthesia in the soft palate [57].

The implantation of the Pulsante® often requires the expertise of a maxillofacial surgeon because of the approach. It remains a minimally invasive surgery, but it exposes to damage of maxillary branch of the trigeminal nerve with a risk of sensory disturbances and possibly neuropathic pain. In the PATHWAY CH-1 study, 81% of patients experienced transient, mild-to-moderate hypoesthesia within the maxillary (V2) nerve territory, resolving within 3 months in most of the cases [55]. More recently, the safety of the surgical implantation procedure has been evaluated

in a cohort of 99 patients, including 43 patients of the PATHWAY CH-1 study and 56 patients from the Pathway-R1 registry [58]. Eighty-one percent of the patients experienced at least one adverse event, most of them being transient. Sensory disturbances were the most frequent complications, observed in 67% of the patients, 46% of them resolving within a mean delay of 104 days. Transient allodynia was rare (3%). Pain and/or swelling was reported by 47% of the patients, resolving in 80% of the cases with a mean delay of 68 days. Dry eye (3%, resolving in 40% of cases), transient trismus (8%), and limited jaw movements (6%) were also reported. Infection rate was 5%. Device revision procedures were performed in 13 cases due to inappropriate initial placement of the stimulating electrode within the PPF. Five devices were explanted. Although frequent, most (92%) of the adverse events were transient and evaluated as mild or moderate. The authors concluded that Pulsante® insertion procedure has sequelae comparable to other oral cavity surgical procedures. Moreover, the technique is recent, and the rate of surgical complications will likely decrease with progression of the learning curve, further refinement of the surgical procedure and tools, and the use of neuronavigation systems [59].

13.4.4 Mechanisms of Action

The mechanism of action of the SPGS by Pulsante® is supposed to be the parasympathetic inhibition. This inhibition appears secondary to the high-frequency stimulation generated by the Pulsante®, and it has been shown that, conversely, the SPGS using a low-frequency stimulation was likely to trigger attacks in subjects with CH [60].

13.5 Conclusion

Substantial progress has been achieved in invasive and noninvasive neuromodulation techniques to treat cluster headache, but evidence for using such approaches was relatively sparse. This weak evidence had been outlined by the European Headache Federation in a consensus statement [28]. According to this international consensus, the application of an invasive neuromodulation, either in a trial or on the basis of a CE mark treatment, should be considered only once all alternative therapies as recommended by international guidelines have failed. This implies that the patients have been evaluated in a tertiary care headache center. When invasive neuromodulation technique is indicated for a refractory chronic CH patient, it is advisable to use ONS and SPGS before considering DBS. nVNS is an attractive treatment option with excellent safety profile, and, if its efficacy is confirmed, it should be used prior to surgical implantation of a neurostimulator in refractory chronic CH and eventually considered as an adjunctive treatment in less severe CH.

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