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Review Article

Neuromodulators for Primary Headache Disorders: A Review

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Received: July 10, 2020; **Published:** July 28, 2020

Abstract

Primary headache disorders are among the most common and disabling globally. Pharmacological treatments are often insufficient, poorly tolerated, have side effects and the majority of patients are unable to complete their treatment. Understanding the neural pain pathways of these disorders has led to the development of alternative therapies. Electrical nerve stimulation is a form of pain modulation with few side effects for the treatment of primary headache disorders. Different neuromodulation approaches, both invasive and non-invasive, have rapidly led to new approaches for the treatment of patients suffering from headache, particularly those who have failed traditional pharmacotherapy. Non-invasive treatment methods are safe, practical and well-tolerated compared to alternatives. This paper details recent evidence-based advances in neuromodulators for primary headache disorders such as migraine and trigeminal autonomic cephalalgias (in particular, cluster headache) including non-invasive commercial devices used for migraine and cluster headache. The target neural structures, their advantages and disadvantages and their application in headache treatment are discussed. Examples of using neuromodulation to manage primary headache disorders are discussed. Both invasive stimulations e.g. of occipital and vagus nerves, the sphenopalatine ganglion, deep brain and spinal cord, and non-invasive, e.g. stimulation of the frontal, cervical and auricular vagus nerves, transcranial magnetic and transcranial direct current stimulation, are detailed.

Keywords: *Cluster Headache; Migraine; Neuromodulation Devices; Neurostimulation; Primary Headache*

Abbreviations

CE: Conformité Européenne; DBS: Deep Brain Stimulation; FDA: Food and Drug Administration; i-ONS: InvasiveoOccipital Nerve Stimulation; i-VNS: Invasive Vagus Nerve Stimulation; SCS: Spinal cord Stimulation; SPGS: Sphenopalatine Ganglion Stimulation; TACs: Trigeminal Autonomic Cephalalgias; t-aVNS: Transcutaneous Auricular Vagal Nerve Stimulation; t-cVNS: Transcutaneous Cervical Vagal Nerve Stimulation; t-FNS: Transcutaneous Frontal Nerve Stimulation; t-DCS: Transcranial Direct Current Stimulation; t-MS: Transcranial Magnetic Stimulation

Introduction

The two primary headache disorders are migraine and trigeminal autonomic cephalalgias (TACs) headaches; they are the most common disorders and leading causes of disability worldwide. Migraine is characterized by a recurrent, unilateral or bilateral throbbing headache, which is usually accompanied by nausea, photophobia and phonophobia [1]. It is the third most common neurological disorder and the seventh most frequent cause of disability which affects an estimated one in six of the population. Migraine prevalence varies between 2.6% and 21.7% with variations between countries and in different studies [2]. It is common amongst the European population and is

estimated at 15% in adults [3]. In American society, it affects almost 20% of the population [4] and has remained stable over many years. The prevalence of migraine across different continents is shown for both males and females in figure 1 [2,5]. Its effects can persist over the productive life of an individual and affect the ability to work or carry out activities during daily living. During migraine attacks, only 25% of patients can function without help from others. The rest need help with their daily activities which result in a loss of about 20 million working days a year [2,5]. In terms of headache duration, migraine may be divided into episodic migraine and chronic migraine. Episodic migraine occurs on less than 15 days per month. Cluster headache is defined as occurring on 15 or more days per month for more than three months, with the condition that the headache has the features of migraine for at least eight days per month [6].

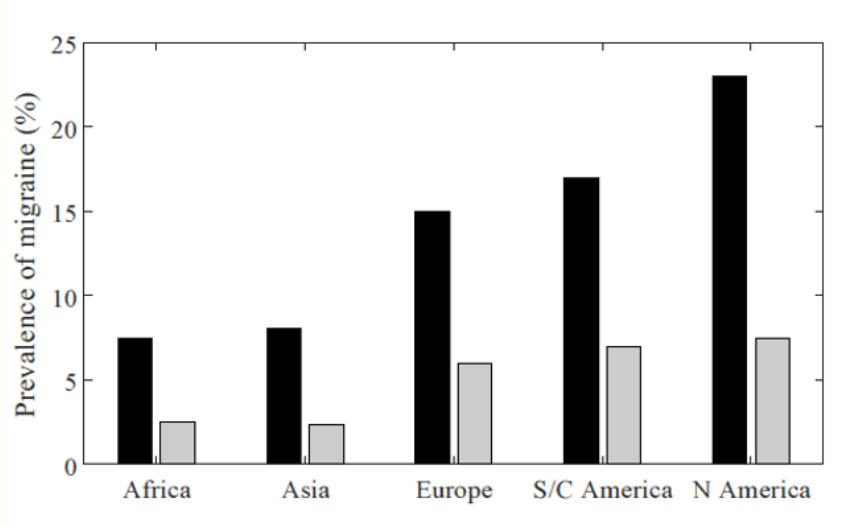

Figure 1: *The prevalence of migraine across different geographic areas and sex, N = North; S/C = South/Central. The prevalence of migraine among females and males are black and grey bars, respectively.*

The TACs are a group of disorders characterised by unilateral head pain occurring in association with prominent ipsilateral cranial autonomic features. The most common type of TACs is a cluster headache. It is a worldwide disorder with a prevalence of about 1% in the general population. It is more painful than other types of headache. The pain is severe and mostly one-sided. The location of the pain is orbital, supraorbital, temporal or in any combination of these sites. The pain lasts for a short time; generally, 15 - 180 minutes and occurs from once every other day to eight times a day. CH may be associated with one or more of the following symptoms: conjunctival injection, lacrimation, nasal congestion, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and/or with restlessness or agitation [5,7].

Available pharmaceutical treatments of primary headache can have moderate to severe side effects, including headache chronification due to overuse [8]. These may lead to inefficacy, dissatisfaction and/or abandonment of medication. In a recent study [9], 80% of patients do not continue their migraine treatment beyond one year, and four in five of the patients would like to have an alternative to pharmaceutical therapies due to their lack of efficacy or their side effects [10]. Electrical nerve stimulation is an approach of pain control which has few side effects, using either surgically implanted (invasive) or transcutaneous (non-invasive) neuromodulation devices to stimulate the targeted nerve to interfere with normal sensory perception, leading to pain relief.

A recent study [15] has shown that neuromodulation can be a viable alternative treatment. Neuromodulation is defined as the process of inhibition, stimulation, modification, regulation or therapeutic alteration of activity, electrically or chemically, in the central, peripheral or autonomic nervous systems [5]. There are a variety of central and peripheral nerve stimulation methods that have been studied, and these techniques have offered at least some improvement. There is increasing interest in using neurostimulation to treat headache disorders. Neuromodulation treatments are grouped as invasive and non-invasive. They can be classed as peripheral or central regarding their effect on the neural circuitry. The peripheral neurostimulation is applied to peripheral (pericranial) nerves. The central neurostimulation aims to activate the central structures (the cerebral cortex). The function of these neurostimulation techniques is to manipulate the central or peripheral pain pathways using electrical or magnetic impulses to provide preventative or acute treatment. The preventative treatment suppresses the central sensitisation of primary headache disorder, while the acute treatment blocks the processes which are responsible for generating attacks.

Several invasive and non-invasive neuromodulation devices have been developed for the treatment of migraine and cluster headache. Some of these are Conformité Européenne (CE) marked or US Food and Drug Administration (FDA) approved. Most have been evaluated for the prevention of episodic migraine, while some have also been assessed in the prevention of chronic migraine. The exact mechanism of action is not entirely understood, and many studies are small. However, results show a reduction of frequency of headache days per month, as well as a reduction of pain severity, pain duration, and the use of acute medication. Non-invasive neuromodulation devices may be an option for patients who are struggling with tolerating current therapeutics and are not achieving full response to their current medication. They may prefer a non-medication option that helps them reduce acute migraine medication use [11].

This paper reviews five invasive and five non-invasive neuromodulation treatment methods for migraine and cluster headache disorders found in the available literature. However, there are other chronic conditions such as tension-type headache. The designated neural pain modulation pathways of the invasive and non-invasive neuromodulators are identified. Electrical features of available devices, and their target neuro-anatomical structures and possible adverse events are detailed.

Neuromodulation techniques

Invasive (i.e. implanted) methods are occipital nerve stimulation (iONS), vagus nerve stimulation(iVNS), sphenopalatine ganglion stimulation (SPGS), deep brain stimulation (DBS) and spinal cord stimulation (SCS). The non-invasive (i.e. transcutaneous) methods are frontal nerve stimulation (t-FNS), cervical and auricular vagal nerve stimulation (t-cVNS, t-aVNS), transcranial magnetic stimulation (t-TMS) and transcranial direct current stimulation (tTDcS). The underlying principle of non-invasive techniques is to apply the electric pulses through the skin via surface electrodes to depolarize the neural tissue underneath, without requiring any surgery or percutaneous invasive act. This technique is safe and can be used for all primary headache disorders. Patients can purchase or rent such stimulators and can self-administer on a scheduled or as-needed basis.

The drivers for implantable devices are placed under the skin using surgical procedures and are powered either wirelessly or by implanted batteries, with leads going to the appropriate nerve targets. The settings of these devices can be changed remotely or by further surgery. Their possible neuro-anatomical targets are cerebral cortex, the high centre of the brain, trigeminal nerve branches, vagus and occipital nerves, and the trigeminal nucleus caudalis in the high cervical spinal cord [12-14].

Non-invasive neuromodulation alters neural activity by the stimulation of nerves or neural tissue from the skin surface. This technology is emerging as a practical and safe alternative to conventional pharmacological interventions for the treatment of migraine and cluster headache. The demonstrated efficacy and safety of several non-invasive neuromodulation therapies have generated interest among clinicians and patients. The clearance of these therapies by European CE mark and the FDA provides an alternative for the treatment of primary headache [15].

Invasive neuromodulators

Invasive neurostimulation treatment requires surgery with its element of risk. Thus, they may be only used for those chronic patients who fail to respond to existing preventive drugs or fail to tolerate them, and, if applicable after trying non-invasive neurostimulation treatment [12].

Subcutaneous stimulation consists of several components: electrodes and their leads (bundle wires), anchors to fasten the leads to the associated tissue and a power source. Generally, there are two types of electrode leads in peripheral stimulation. These are percutaneous leads which are thin and cylindrical and paddle leads which are flat and broad. The electrodes are metallic points on the lead, which are generally made of platinum-iridium. These contact points can be designated as anodes or cathodes to convey the current to the target structure. One of the main differences between lead and paddle electrodes is that the leads can be inserted with the aid of a needle.

In contrast, surgical dissection is required for paddle electrodes. In both cases, the power source for peripheral nerve stimulation is typically implanted in a subcutaneous pocket which is similar to pacemaker battery. The paddle electrode is shielded on one side, and the percutaneous lead electrode is not. As a result, the current is directly transmitted through the target structure across to the percutaneous lead. This requires lower current levels to activate the neural structure, which allows longer battery life. Both electrode types have been used for stimulation.

The available options for a power source are an external radiofrequency (RF) transmitter/receiver system, an implantable rechargeable cell and pulse generator. The RF receiver can be powered from an external RF transmitter coil placed on the skin over the device. Current batteries are rechargeable with a lifespan close to 10 years. The typical implant locations in the body are upper buttock, abdomen and upper chest [16,17]. The available invasive neurostimulation therapeutic procedures for migraine are shown in figure 2.

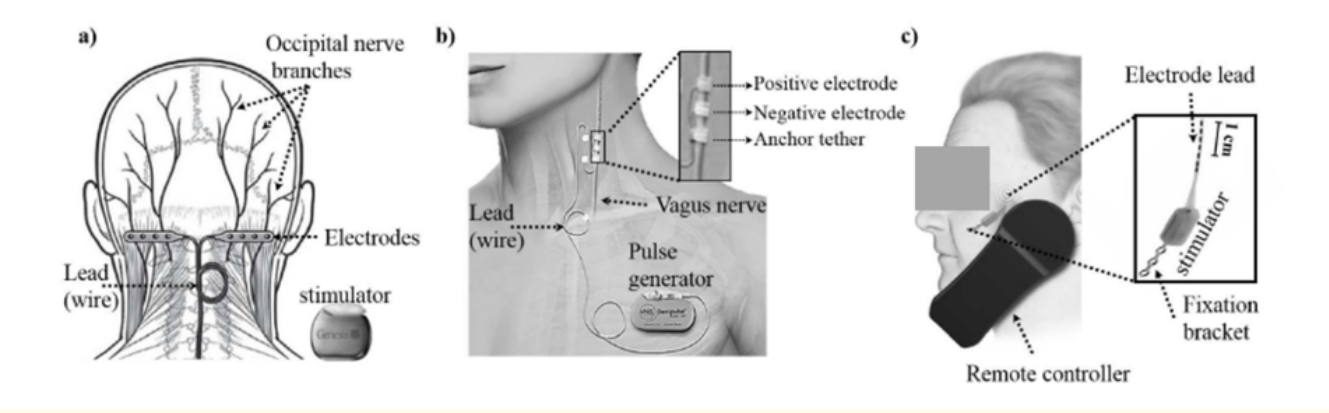

Figure 2: *Available invasive neurostimulation procedures. (a) Shows invasive occipital nerve stimulation (i- ONS) where electrodes are placed on the branches of the occipital nerve at the back side of the head. Two leads are used to cover both sides of the neck. A small pocket is implemented in the subcutaneous tissues around the incision where the leads will be looped and anchored. (b) Shows placement of the vagus nerve stimulation device, a pulse generator is implanted in the tissues of upper chest and electrical pulses are transmitted to the associated nerve via electrode leads. The end of the electrode helical lead is wrapped around the nerve and helps to anchor the lead to the vagus nerve. (c) The sphenopalatine ganglion (SPG) microstimulator implanted with an integral lead and a battery. The lead is placed within the pterygopalatine fossa structure. The microstimulator can be controlled by a hand-held remote control device. Figure adapted from [5].*

Occipital nerve stimulation (iONS)

The iONS has matured significantly over the past half-century developing a better understanding of its potential therapy and the implant techniques necessary for a successful outcome [18]. It has been used to treat migraine and cluster headache disorders by suppressing the peripheral and central pain mechanism [19]. Although the exact mechanism of the iONS is not fully understood, an animal study showed that it has an antinociceptive effect on the trigeminal nerve fibers second-order neurons in the trigeminal nucleus caudalis [20]. Although the iONS is regarded as a costly treatment method with significant implementation complexity, it has been shown that using this treatment provides promising results for both chronic migraine and cluster headache disorders [19] nerve block [21] and neuroimaging studies [22] provide evidence that iONS is able to modulate both peripheral and central pain-controlling areas. Many iONS trial studies indicate at least some improvement in chronic cluster headache and a further large randomised controlled trial is under way [23]. Other results suggest that iONS can be used as an alternative solution for patients where non-invasive and pharmaceutical procedures have failed to provide any substantial improvement [24].

The target neuroanatomical structure for i-ONS stimulation is the greater occipital nerve. The stimulating electrodes are implanted subcutaneously in the occipital region surgically to activate the greater occipital nerve and lesser occipital nerves. Note that the electrode leads can be either placed on the target structure or, to minimise invasion can be implanted just above it to propagate electrical impulses in the neural tissue. In current designs, patients can adjust their stimulation intensity levels using a hand-held remote control. The stimulator device is often implanted under the collarbone (clavicle), but the abdominal and buttock (gluteal) areas are also options. The optimum settings for iONS are not yet defined and there is a wide variation in the stimulation settings used.

The most common adverse events of the iONS are lead migration, battery depletion, and infection, which may require additional surgery. Other complications are painful stimulation, pain over the battery site, paresthesia intolerance and hardware related adverse events. In a large population study [24] among the patients who had iONS treatment for migraine, 40% of them underwent additional surgery and 70% of them experienced at least one adverse event.

Vagus nerve stimulation (iVNS)

The iVNS technique has been used in the treatment of refractory epilepsy and depression. Experiments on animals showed that stimulation of the vagus nerve aborted or reduced their frequency. There are many small studies about the efficacy of the iVNS for epilepsy, which showed that that iVNS provided efficacy benefits in migraine management, especially for cluster headaches. In another study, it has been demonstrated that using iVNS provided a positive impact on the patients who have cluster headaches and cluster headache [25,26].

In iVNS, the stimulating electrodes are implanted and wrapped around the vagus nerve in the neck. The current pulse generated by a pacemaker-like device (generator) is transmitted through a flexible wire (lead). The vagus nerve consists of both motor (80%) and sensory fibers (20%). The stimulating mechanism of iVNS in the treatment of migraine disorder is not fully understood. However, it is postulated that nociceptive transmission may be modulated through the activation of vagus nerve afferents that go to the higher centre of the brain through the trigeminal nucleus caudalis. This may explain the effect of the iVNS on headache, ultimately through a reduction of glutamate levels and neuronal firing in the spinal trigeminal nucleus. These potential mechanisms need to be examined. The efficacy of iVNS for migraine needs appropriately designed, randomised, sham-controlled studies.

The common adverse events of this method are surgical infection, temporary excessive salivation, permanent voice alteration, mild coughs, paralysis of the vocal cord, lower facial weakness and the coercive feeling of coughing. The battery of the stimulator may need replacement necessitating additional surgery. Although stimulation of the vagus nerve has a role in the reduction of migraine pain, the potential associated risks and the high cost limits the use of the procedure [5,24,27].

Sphenopalatine ganglion (SPG) stimulation

The SPG is the largest extracranial structure. It is situated in the pterygopalatine fossa and has a connection with the trigeminal nerve and multiple neural roots. Since SPG is relatively close to the skin surface and therefore, less invasive, it has been the target for neuromodulation in the treatment of different types of headache for many decades [28]. Controlled studies have shown that the electrical stimulation of the SPG appears to be an effective treatment for patients with chronic cluster headache. They suggest that many patients were released from the pain, and SPG provides a significant reduction in pain frequency in cluster headache relief for patient group [19].

Although electrical stimulation of the SPG is mostly used for cluster headache [29], it has also shown a degree of pain frequency reduction in migraine [30]. Sphenopalatine ganglion stimulation has been provided in a commercial device, the Pulsante device (Autonomic Technologies, Inc., Redwood City, California, USA) which is a miniaturised implantable neurostimulator with integral lead and battery. It is currently approved in Europe for the treatment of primary headache disorders [14]. The stimulator uses multiple electrodes, and all the features of the neuromodulator are adjustable, including location, duration, and intensity of stimulation, frequency and the bandwidth of the stimulation signal. The electrodes and pulse generator are implanted through the mouth above the teeth and screwed to the skull. Although the neurostimulator and electrode arrangements are implanted, the power is supplied by a small wireless handheld remote controller. The efficacy of the SPG neuromodulator is low and has limited safety due to subcutaneous implantation. The most common hazards of this method are hardware failure, mild-to-moderate hypoesthesia within the maxillary nerve territory, sensory disturbances, limited jaw movements and dry eye [31,32].

Deep brain stimulation (DBS)

The DBS has shown some success in preventing pain attacks when treating chronic headache patients, although there is a lack of control studies [32]. It is assumed that there is a link between hypothalamus and pain modulation of the cluster headache. Deep brain stimulation positron emission tomography studies showed that activation was observed during cluster headache attacks [33]. It is postulated that the cluster pain attacks can be reduced by using DBS at high frequency. The optimal target for DBS for refractory chronic cluster headache is shown in [34].

The DBS neurostimulator is usually placed under the skin near the collar bone or in the chest. An extension wire is inserted under the skin in the neck and shoulder, and the tip of the electrodes are positioned on the hypothalamus [19]. There are serious risks in addition to the complexity of the invasive procedure, although they are lessening with improved DBS procedures. These are: transient loss of consciousness, transient diplopia, death due to intracerebral haemorrhage, infection sometimes necessitating removal of the DBS system and electrode displacement. Due to its invasiveness and side effects, DBS should be considered only for the most severely affected patients with cluster headache after all other available treatments have been tried [19,34].

High cervical spinal cord stimulation (SCS)

The SCS has for a long time, been successfully employed in a variety of neuro-pain modulators. It has been shown that patients treated with SCS have improved pain relief, quality of life and functional capacity and greater treatment satisfaction compared to those patients treated with conventional medical treatment for pain disorder [35,36].

High cervical spinal cord stimulation technique is similar but riskier than i-ONS. The latter is an emerging approach for the treatment of chronic migraine and chronic cluster headache. High cervical spinal cord stimulation uses implanted leads to deliver electrical stimulation to the trigemino-cervical complex. The leads are introduced using a needle into the upper thoracic epidural space and then advancing the leads through the needle superiorly until the tip of the electrodes. First, the stimulator leads are placed and connected to a battery powered source. The system is tested outside then implanted once there is positive feedback from the patients. A recent study [35], showed that using high cervical SCS reduced chronic cluster headache pain attacks after a prescribed test time. All participants re-

ported paraesthesias in the trigeminal region, suggesting that stimulation of the high cervical spinal cord can provide both trigeminal and cervical neuromodulation. High cervical spinal cord stimulation has also been studied for the treatment of medically intractable chronic migraine [37]. It has been shown that this method may offer a promising treatment alternative for patients with intractable chronic migraine. In a difficult-to-treat cohort of patients with intractable chronic cluster headache, the effectiveness of high-cervical SCS was equal or better than that of iONS in patients with chronic migraine but at the expense of a higher rate of adverse events, mainly related to lead position adjustments [37].

Non-invasive neuromodulators

Several commercial transcutaneous neuromodulation devices are available to treat migraine and cluster headache. Most of them are currently approved for the treatment of migraine, and there is one (GammaCore) for the treatment of cluster headache. Table 1 summarises the technical specifications of non-invasive neurostimulation devices and can be read in conjunction with figure 3. The exact mechanisms of action are not entirely understood but results of many studies show a reduction of frequency of headache days per month, as well as a reduction of pain severity, pain duration, and reduction of the use of acute medication. Transcutaneous neuromodulation devices may be an alternative for patients who are struggling with tolerating present pharmaceutical and implantable therapeutics.

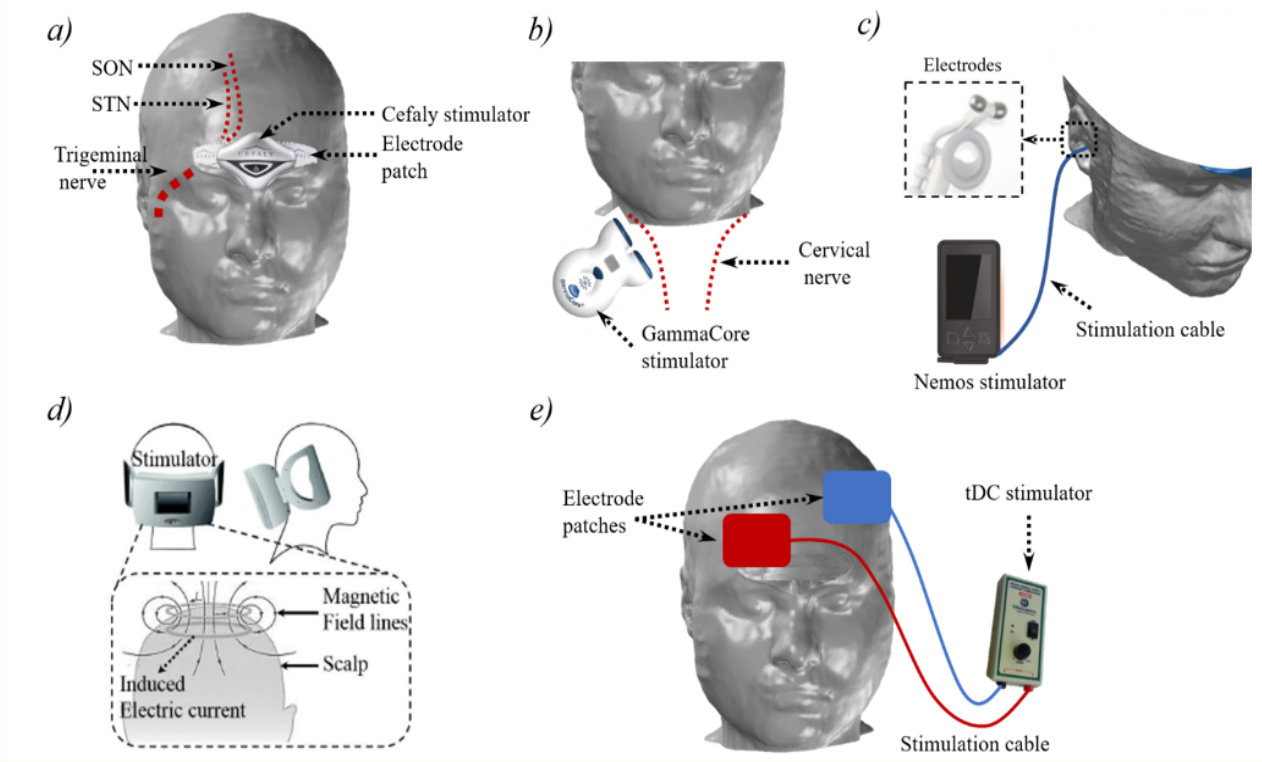

Figure 3: *Available non-invasive neurostimulation devices. (a) Shows Cefaly stimulator which is placed over the forehead and covering frontal nerve. The user can control the stimulator manually. (b) Shows GammaCore device, the electrode is applied on the neck via gel. (c) Shows Nemos device which has mobile phone-like stimulator. The user can control the stimulator manually. (d) Shows SpringTMS device, the magnetic field is applied by coils through the back of the head. (e) NeuroConn stimulator device which aims to change the cortex excitability using relatively large electrodes. All devices can be controlled by patients.*

Device	Use	Electrode	Intensity	Frequency	Pulse Width	Stimulation Wave	Source
Cefaly	Migraine	Bipolar	1 - 16 mA	60 Hz	250 μs	Biphasic	[41]
Nemos	Cluster headache	Bipolar	25V	10 Hz	0.3 ms	Biphasic	[36]
GammaCore	Cluster headache, migraine	Bipolar Disc	≤ 24V	25 Hz	1 ms	Biphasic	[24]
SringTMS	Migraine	Bipolar Disc	4 mA/cm^2	-	180 μs	Biphasic	[5]
NeuroConn	Migraine	Bipolar Rubber	< 4.5 mA	Adjustable	Multiple	Multiple	[45]

Table 1: *Non-invasive neurostimulation devices.*

The frontal neuromodulator from Cefaly, (CEFALY Technology, Liège, Belgium) was originally approved for the prevention of migraine and has received further approval for acute use. The Cefaly stimulator, which patients wear across the forehead, has been developed to stimulate the supraorbital and supratrochlear nerves [38]. The SpringTMS device is a rechargeable handheld device that delivers a single pulse of magnetic stimulation to the back of the head to treat migraine. The GammaCore device is a handheld transcutaneous cervical vagus nerve stimulator applied to the neck and is the first approved for the treatment of the episodic cluster headache. The GammaCore and Nemos have been used as the treatment for non-invasive VNS. The GammaCore consists of placement of a handheld device on the lateral side of the neck and transcutaneously sending pulses of mild electrical stimulation to the cervical branch of the vagal nerve to treat cluster headache and migraine. The NEMOS is a portable and easily operated stimulator that targets the stimulation of the auricular branch of the vagus nerve for treatment of chronic migraine and epilepsy [19]. The NeuroConn stimulator has a controlled constant current stimulator that aims to treat episodic migraine. It provides cortex excitation using large electrodes. The safety of the device is controlled by a microprocessor monitor based on the multistage monitoring of the current path using advanced hardware and software combination [11].

Transcutaneous frontal nerve stimulation (t-FNS)

The trigeminal nerve has a crucial role in headaches [39]. The supraorbital nerve (SON) and supratrochlear nerve (STN) arise from the frontal branch of the ophthalmic division of the trigeminal nerve that innervates the frontal sinus, upper eyelid and anterolateral part of the forehead and scalp. The t-FNS by the Cefaly stimulator has been developed to prevent episodic migraine by stimulating the SON and STN, as shown in figure 3a [40,41]. There is currently no evidence to support the use of transcutaneous nerve stimulation in cluster headache [42]. The Cefaly device is a battery powered supraorbital nerve stimulator. The electrodes are applied to the forehead using a headband. The neuromodulator settings can be customised or controlled based on the patient's needs. The Cefaly generates electrical pulses and transmits them via a self-adhesive supraorbital electrode to excite on the SON and STN located under the skin of the forehead, as shown in figure 3a. 60 Hz low-frequency symmetrical rectangular biphasic stimulation pulses are applied through the electrodes. The current pulse amplitude can be varied between 1 and 16 mA, depending on the patient's sensation of tingling on the forehead. Although the exact pain mechanism of this method is unknown, it is believed transcutaneous electrical nerve stimulation with Cefaly neurostimulator may stimulate these nerve pathways acting therapeutically on the inhibitory circuit in the trigeminal nucleus caudalis [41] and pain may be inhibited by activation of Aβ to inhibit the nociceptor fibres (Aδ and C). Another possible mechanism in pain attacks may be reduced by neural plasticity. The effectiveness of t-FNS in an episodic migraine was evaluated in a randomised double-blinded and sham-controlled study with a positive response rate of 50%. A post-marketing survey of 2313 subjects using the Cefaly device, as a preventative treatment of episodic migraine, reported 53.4% satisfaction with the procedure. This was deduced from the number of subjects continuing the treatment after a 40-day trial period [41]. 46.6% of the patients were not satisfied with the Cefaly device (among them, 40% of patients using the device at least 20 days) [41]. These results can be associated with the often required high current levels due to the variations of the neuroanatomical structures and electrode arrangements causing discomfort [40]. The efficacy of Cefaly is nearly the same as topiramate

(one of the best preventive medicine for episodic migraine and Cefaly has better safety. Thus, Cefaly may be superior for episodic migraine prevention when safety and efficacy are considered together. FDA approved the Cefaly as the first medical device for prevention of migraine. The most common complications reported are pain and paresthesia induced by the stimulation [5].

Transcutaneous cervical VNS (t-cVNS)

The vagus nerve contains both motor and sensory components and has a role in pain management. The development of non-invasive transcutaneous vagal nerve stimulator devices such as the GammaCore device (electroCore LLC, Basking Ridge, New Jersey, USA) is a handheld device that provides transcutaneous stimulation of the cervical branch of the vagus nerve to modulate primary headache. This therapy is administered with a handheld device which is placed on the neck to activate the vagus nerve through the skin, as shown in figure 3b. The available literature on transcutaneous vagal nerve stimulation using the GammaCore device suggests that at present, it could be considered for the use of prevention of chronic cluster headache. There is, as yet, insufficient evidence for transcutaneous vagal nerve stimulation for acute or preventative treatment of migraine or the acute treatment of cluster headache. From current evidence, there is not a role for invasive vagal nerve stimulation in the treatment of primary headaches [24,42].

Although the device was initially approved to treat cluster headache, small studies have shown there was some improvement in migraine pain as well. However, the devices are not FDA approved. Most of the reviews on using this procedure have no control group. For objective, safe and well-evidenced results, long-term randomised control studies of t-cVNS are required, and the exact underlying mechanism of the pain remains unclear. The adverse events are local discomfort, mild skin irritation, worsening pain [24].

Side effects reported by people using GammaCore include discomfort and redness at the site of use, dizziness and a tingling sensation. The GammaCore device has not been studied in children or women who are pregnant, and it is not considered safe for people who have an implantable medical device, carotid atherosclerosis, or who've had a cervical vagotomy (surgery to cut the vagus nerve in the neck) [5].

Transcutaneous auricular VNS (t-aVNS)

The neuromodulation treatment featuring the most investigation for cluster headache treatment is noninvasive, external vagus nerve stimulation (nVNS), which is now FDA cleared for both the acute treatment of episodic cluster headache attacks and as adjunctive therapy for cluster headache prevention [11]. For the acute treatment of episodic cluster headache, nVNS is effective, well-tolerated, and licensed [11].

One of the VNS treatment methods aims to treat or reduce pain attacks of cluster headache and migraine by applying stimulation to the left auricular branch of the vagus nerve fibres (thick myelinated sensory Aβ fibre afferents) based on transcutaneous electrical nerve stimulation technique. A recently developed medical device (NEMOS, cerbomed, Erlangen, Germany) provides transcutaneous stimulation of the auricular branch of the vagus nerve using a particular ear electrode as shown in figure 3c. The device has received the CE mark for treatment of pain. The literature on the therapeutic effects of auricular stimulation on the symptoms of several disorders is expanding. The battery-driven neuromodulator has electrodes placed in contact with the skin of the conch near the ear. The electrical pulses from the stimulator have the following characteristics: pulse width: 250s, frequency: 1Hz or 25Hz, duty cycle: 30s on, 30s off, to avoid habituation) released from the stimulator during stimulation. The individual can increase the stimulus up to the point when tingling sensations occur [5,36].

A recent control study showed that daily treatment with t-aVNS is useful in chronic migraine. Although t-aVNS stimulates only vagal afferents, there are close connections between afferent and efferent parasympathetic brainstem centres, suggesting a likely influence of VNS on dural efferents. A significant practical advantage of t-aVNS is good patient tolerance and safety. Another advantage of t-aVNS therapy is that it can be combined with any other drug treatment without risking cumulative adverse effects or pharmacodynamic interactions.

Also, t-aVNS allows patients to continue routine activities, leading to high compliance with stimulation times (around 85% on average). However, long-term effects and sustainability of efficacy of t-aVNS are still unknown and need to be demonstrated in appropriate open-label trials [43].

Side effects include mild skin irritation, muscle (sternocleidomastoid) contraction, stiff neck, frequent urination, shoulder pain, neck twitching, raspy voice, lip or facial drooping, and redness [36].

Transcranial magnetic stimulation (t-MS)

It has been proposed that patients with migraine have a state of abnormal brain hyperexcitability, and this theory is supported by transcranial magnetic stimulation studies [42].

t-MS activates the human motor cortex based on the principle of electromagnetic induction which has the effect of changing the firing pattern of neurons. t-MS has been shown to disrupt the wave of cortical spreading depression, which is thought to be the experimental correlate of migraine aura. The current pulse of adjustable amplitude and width passes through a coil located within the neuromodulator. The coil position results in an electromagnetic field located within a target area where induced currents affect various neurotransmitter levels, as shown in figure 3d. Animal studies have shown the nociceptive trigeminothalamic neurons can be inhibited by this approach [44]. A portable neuromodulator (SpringTMS) (Figure 3d) has been developed to reduce acute migraine pain levels. It is shaped to cradle the back of the head while being held with both hands. This single-pulse transcranial magnetic stimulator was explicitly designed for migraine treatment. The device applies a single magnetic pulse to the scalp and underlying cortex resulting in induced electrical field generation in the cortex. The primary cause of a visual aura that precedes a migraine headache is a wave of depressed nerve activity in the brain that sweeps across the cortex, called cortical spreading depression (CSD). The SpringTMS device uses magnetic energy to disrupt this wave when used within one hour of the onset of an aura. According to a post-marketing survey, the majority of the patient population were not satisfied, possibly due to inadequate benefit, cost or inconvenience [42]. The patient groups who completed the survey reported some reduction in migraine and some reduction in attack duration. However, there is no controlled evidence to support the use of the t-MS device in the prevention of migraine.

The common complications are transient and mild; these include dizziness, lightheadedness, tingling and worsening of migraine pain. Also, this method cannot be applied to those patients who have epilepsy, skull defects or have a pacemaker, cardiac lines, metal in the head (electrodes, stimulation devices) or other apparatus that could be influenced (dislocation, induction of electric currents) by a magnetic field [44].

Transcranial direct current stimulation (t-DCS)

The t-DCS is a neuromodulation technique that has been studied for the prevention of episodic migraine. t-DCS can modulate pain-related neural networks. It has also been shown to allow a reduction of analgesic drug intake and has minimal adverse events [11].

The t-DCS can modulate cortical excitability by an anodal (excitatory), or cathodal (inhibitory) electric current applied to the scalp A portable neuromodulator (NeuroConn) (Figure 3e) has been developed. In this device, a weak current (e.g. 1 - 2 mA) is applied by relatively large electrodes that are placed on the scalp as shown to modify the membrane potential which alters cortical excitability and activity depending on the current flow direction through the target neurons [45]. The system can be modified using multiple and variable design features (different size of electrodes and electrical features of the stimulation based on the patient needs). This procedure can induce neural plasticity. Although there are limited studies which investigate the effectiveness of t-DCS on migraine, it has been suggested that t-DCS may have a positive impact on migraine (reduced pain intensity). The limitations of t-DCS are mainly the use of large electrodes resulting in low spatial resolution and difficulty in defining the treatment protocol (e.g. localisation, current density and electrodeposition). Further large randomised controlled studies are necessary to optimise the correct stimulation settings [46].

Complications experienced are unpleasant sensations after t-DCS, a mild tingling sensation occurring directly under the electrode, moderate fatigue and occasional headache. Although most of the adverse effects are mild and disappear soon after stimulation, several papers have reported that some, most commonly skin problems, can persist even after stimulation.

Conclusion

Neurostimulation is emerging as a promising treatment option, particularly for medically intractable chronic primary headache. Neuromodulation can be delivered invasively, but this exposes patients to the associated risks. The non-invasive treatment option is a relatively safe and reversible treatment option for these various headache conditions, especially as the protocols are refined to ensure improved outcomes. Although invasive options have a positive impact on patients, these neuromodulation methods should be reserved for patients with medically refractory headaches, in particular chronic cluster headache. Although both ONS and SPGS techniques are invasive, they are recommended as first-line therapy in refractory cluster patients. DBS is considered a third-line treatment in cluster headache because of its potentially life-threatening side effects.

Several non-invasive neuromodulation approaches for the treatment of primary headache disorders are already available, and ongoing studies will shed light on the most appropriate indications for these interventions. Currently, t-FNS and t-TMS are FDA and CE approved and commercial devices are available for migraine prevention. VNS is CE and FDA approved for cluster headache, but CE approved for migraine prevention. However, current evidence shows that the quality of the available therapeutic effects is limited, and there is a need for large randomised controlled trials for better-defined outcomes.

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