

Review

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Neuromodulation in the Treatment of Migraine: Progress in Nerve Stimulation

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Orlando, Florida, USA***ABSTRACT**

Migraine is a type of primary headache disorder that can become chronic and disabling. The exact pathomechanism of migraine is not known very well and its treatment is also difficult in some cases. There are several medications for the acute and preventive treatment of migraine including the “triptan” family drugs, nonsteroidal anti-inflammatory drugs, anti-epileptic drugs, beta-blockers, and Ca²⁺-channel blockers¹ and those against calcitonin gene-related peptide or its receptor that are reviewed elsewhere.² However, there are some medically intractable headaches or patient management is unsatisfactory or medications are poorly tolerated³ or there are contraindications. Therefore, neuromodulation and nerve stimulation methods that have proven effective in clinical research may provide an additional treatment option for acute and preventive treatment of migraine. In this brief review, we will discuss recent advances using neuromodulatory techniques that are currently used in the treatment of headaches in clinical studies. These include the electrical stimulation of occipital nerve, sphenopalatine ganglion, supraorbital nerve, and transcutaneous electrical stimulation of vagus nerve as well as single-pulse transcranial magnetic stimulation. Several clinical studies have conducted neurostimulation for the acute and preventive treatment of migraine in recent years but more studies are necessary to see their efficacy and long-term effect.

KEYWORDS: Neuromodulation; Migraine treatment; Nerve stimulation.**ABBREVIATIONS:** AED: Anti-epileptic drugs; CGRP: Calcitonin gene-related peptide; CNS: Central Nervous System; CM: Chronic Migraine; fMRI: Functional Magnetic Resonance Imaging; GABA: Gamma amino butyric acid; HFEM: High Frequency Episodic Migraine; mAbs: Monoclonal antibodies; NSAIDs: Nonsteroidal anti-inflammatory drugs; nVNS: Non-invasive vagal nerve stimulation; ONS: Occipital Nerve Stimulation; PET: Positron Emission Tomography; SoC: Standard of Care; SPG: Sphenopalatine ganglion; TMS: Transcranial Magnetic Stimulation; TESoSN: Transcutaneous electrical stimulation of supraorbital nerve; VNS: Vagus/Vagal Nerve Stimulation.**INTRODUCTION**

Migraine is a disabling brain disorder that is believed to be due to the dysfunction of the sub-cortical structures including diencephalic and brain stem areas that are involved in the processing and modulation of painful stimuli, leading to a dysmodulation of pain and vascular tone especially in the trigeminovascular system of susceptible patients.⁴⁻⁸ There are two types of migraine: Migraine without aura and migraine with aura that occurs in about 30% of the migraine patients.⁹ Activation of cortical neurons, the cortical spreading depression of Leão has long been proposed for the pathophysiology of migraine with aura^{10,11} and a number of genetic abnormalities (channelopathies) have been detected in migraine patients with aura.¹²⁻¹⁷ Migraine is a disabling disorder characterized by a unilateral pulsatile headache that is often accompanied by nausea and vomiting and lasts for 4-72 hours.¹⁸ Migraine is a multifactorial disorder that is more common in females and is sometimes associated with comorbid disorders such as depression and epilepsy.¹⁹ Genome-wide association studies have shown 13 migraine-associated variants that are involved in synaptic function, glutamatergic neurotransmission, nociception,

vascular physiology, and metalloproteinases.¹⁹

Migraine can be episodic (frequency of attacks <15 days per month) or become chronic when frequency of the attacks is >15 days per month, 8 days of which have migraine features and the condition lasts more than 3 months.²⁰ Classification of different headache disorders has been continuously updated^{18,20} to better facilitate the diagnosis and treatment of headache. The third edition (beta version) of the International Classification of Headache Disorders²⁰ is an updated source for classification of headache disorders. The exact pathomechanism of migraine is not known and its treatment remains challenging. Some of the main drugs that are currently being used in the acute and preventive treatment of migraine include the “triptans” and nonsteroidal anti-inflammatory drugs (NSAIDs), anti-epileptic drugs (AED), beta-blockers, and Ca²⁺-channel blockers among others.¹ Several neurotransmitters and neuromodulators have been implicated in the pathomechanism of migraine. Among those, calcitonin gene-related peptide (CGRP) is one of the few neuropeptides that has been implicated in the pathogenesis of migraine and its increased level has been detected in the blood of migraine patients with and without aura.²¹ Therefore, some more specific newer drugs such as CGRP-receptor antagonists, known as “gepant” family of drugs such as Olcegepant^{22,23} or Telcagepant,²⁴⁻²⁶ MK-3207,^{27,28} BI 44370 TA,²⁹ BMS-846372^{30,31} and a few others in this category were developed in recent years but were discontinued in their clinical trials phase II and III or at an earlier stage mainly because of their liver toxicity and other problems. A recent double-blind, placebo-controlled, phase II b clinical trial randomized 834 participants to treat one migraine attack with various doses of Ubrogepant (MK-1602).³² In that study, 527 participants received the drug and 113 received placebo. Their result shows that 100 mg ubrogepant was significantly superior to the placebo for causing 2-hour pain-free (25.5% *versus* 8.9%) but not for 2-hour headache response.³² According to that study, this CGRP-receptor antagonist gepant family drug is effective in treating migraine and the adverse events among the ubrogepant and placebo treated patients are similar; therefore, their results seem promising.³²

In recent years, newer (migraine-specific) drugs were developed. These include the 3 monoclonal antibodies (mAbs) against CGRP with long-term effects, the LY2951742,³³ the ALD-403,³⁴ and TEV-48125 (LBR-101)^{35,36} and AMG 334, a mAb against CGRP receptor complex that has been developed by Amgen³⁷ have shown efficacy and tolerability in clinical trials with some minor side effects but are still under examination in clinical trials.

A few other drugs including one acting on 5-HT_{1F} receptor such as Lasmiditan (COL 144) in phase II and III studies³⁸⁻⁴⁰ (that seem promising) and drugs targeting *nitric oxide synthase*, *glutamate*, *acid-sensing ion channels*, or *gamma amino butyric acid (GABA)-A* are still under investigation, please see references^{2,8,41-43} for comprehensive review of the current treatment of migraine.

In spite of several medications available for the prevention and treatment of migraine, invasive and non-invasive approaches such as peripheral nerve blocks, botulinum toxin injection and electrical stimulation of various nerves have gained some focus in the treatment of chronic migraine in recent years. There a number of patients with medically intractable headache syndromes or chronic migraine that are non-responders to medications or poorly tolerate pharmacological medications or have contraindications and may need an alternative therapy.⁴⁴ Therefore, in recent years, neuromodulation and neurostimulation has been examined in a number of clinical studies to test their efficacy and tolerability as a novel method for the acute and preventive treatment of migraine.

This is a brief review of new advances and our current understanding of some invasive (greater occipital nerve or sphenopalatine ganglion stimulation) and non-invasive (transcutaneous vagal or supraorbital nerve stimulation or single-pulse transcranial magnetic stimulation) approaches implicated in the treatment of migraine.

The invasive devices are implanted subcutaneously or through other surgeries and the non-invasive devices are applied on the skin close the nerve and are self-administered by the patient as well. The results of some of these non-medication approaches are promising but more studies and data are needed to understand their efficacy and tolerability and long-term effects and side effects.

ELECTRICAL STIMULATION OF OCCIPITAL NERVE

Electrical stimulation of peripheral nerves for a long-term pain relief in human has been used through implantation of stimulator devices in the body in several clinical investigations for some decade now.⁴⁵⁻⁴⁹

Some of the mechanisms by which electrical stimulation reliefs pain seems to be driven from the well-known “gate theory of pain” and modulation of neurotransmitters release including neuropeptides and GABA-ergic system in the central nervous system.^{50,51}

Electrical stimulation of superior sagittal sinus in cat increased activity in the caudal trigeminal nucleus, the cervical dorsal horn and in the dorsolateral spinal cord at the C2 level showing a convergence of neuroanatomical substrates of head pain on the second order neurons of trigeminocervical system.⁵²

Electrical stimulation of the occipital nerve has shown effectiveness in treating the intractable pain of occipital neuralgias that were refractory to other medications.^{53,54}

One of the first multicenter, randomized, blinded studies for preventive treatment of chronic migraine, the ONSTIM feasibility study, used occipital nerve stimulation (ONS) by means of implantation of a pulse generator device subcutane-

ously superficial to the fascia and muscle layer at the C1 level.⁵⁵ The study assigned 75 out of 110 eligible patients to a treatment group. Their criteria for a responder was a patient who achieved a 50% or more reduction in the number of pain headache days per month or a three-point or more decrease in average overall pain intensity when compared to baseline. That study showed 39% 3-month responders in adjustable stimulation group while the group with preset stimulation or medical management (the control groups) had 6% and 0% 3-month responder rates⁵⁵ raising hope for ONS as a treatment option for some chronic migraine patients.

The other large-scale, multicenter, clinical study using ONS was conducted on 105 chronic migraine patients with active stimulation and 52 with sham-stimulation.⁵⁶ The neurostimulation device was implanted near the occipital nerves. The criteria for responders were those patients that achieved $\geq 50\%$ reduction in mean daily visual analog scale scores by 12 weeks following the procedure.⁵⁶ The study did not meet their own primary endpoint pain criteria and there was not a significant difference in the percentage of responders in the active stimulated group compared with the sham stimulated group. However, there was a significant difference in the percentage of patients that achieved 30% pain reduction. There was also a significant decrease in headache days, and migraine associated disabilities between the active stimulated *versus* the sham stimulated group.⁵⁶ Some other ONS studies did not show a significant difference between the stimulated *versus* sham stimulated groups.³

Similarly, a recent study on 53 patients with chronic migraine (CM) and some with other associated chronic headache phenotypes in addition to CM had similar result; ONS was delivered through implanted device in a single center between 2007 and 2013. Following an average of 42-month follow-up, there was a 45.3% response rate in the whole cohort defined as $>30\%$ reduction in moderate to severe headache days per month, that is 34.3% in the CM group alone and 66.7% in those with multiple headache syndromes.⁵⁷ They also noticed significant reduction in the intensity and duration of pain as well as headache-associated disabilities. The overall mean subjective patient estimate of improvement was 31.7%.⁵⁷

Therefore, although there are some success reports in ONS, at the moment the results are diverse and more studies are necessary to see the efficacy of ONS in the prevention of migraine.⁴¹ More studies using advanced technology in nerve stimulation might have different outcomes as a new study shows better efficacy of burst ONS compared to tonic stimulation in treating animals with trigeminal allodynia.⁵⁸

Consistent with these, customization of stimulation parameters is important in the result of such interventions as suprathreshold stimulation was found to yield better results in the treatment of migraine although subthreshold stimulation was also helpful.⁵⁹

SPHENOPALATINE GANGLION STIMULATION

Sphenopalatine ganglion (SPG) is the largest extracranial parasympathetic ganglion involved in the innervation of meninges, lacrimal gland, nasal mucosa and conjunctiva that all have been implicated in migraine with autonomic cephalic symptoms including lacrimation, nasal congestion and conjunctival injection in common migraine patients.⁶⁰ The postsynaptic projections of the SPG supply lacrimal and nasal glands and are involved in several pain syndromes including trigeminal and sphenopalatine neuralgias, atypical facial pain and headache.⁶⁰ Therefore, blocking SPG has been used to treat atypical facial pain.^{61,62} Involvement of SPG in neurovascular headache has been proposed since early 1900.⁶³

Electrical stimulation of SPG has been also performed for determination of cerebral blood flow and glucose metabolism.⁶⁴

Two mechanisms of action have been proposed for the role of electrical stimulation of SPG in relieving pain. These include possibly the interruption of post-ganglionic parasympathetic outflow, and modulation of sensory processing in the caudal trigeminal nucleus.⁶⁰

A clinical investigation using electrical stimulation of SPG for ≤ 60 minutes in 11 medically refractory migraine patients (one patient was not stimulated) alleviated the pain in only half of the patients⁶⁵ although the failure was attributed to technical problems. The SPG was accessed by a 20-gauge needle through infrazygomatic transcoronoid approach into the sphenopalatine fossa visualized under fluoroscopy; a unilateral electrical stimulation of the SPG was delivered by a Medtronic 3057 test stimulation lead following induction of migraine.⁶⁵ Stimulating parameters in that study were the following: Mean amplitude: 1.2 V, mean pulse rate: 67 Hz, and mean pulse width: 462 micros.⁶⁵

Clinical trials (NCT01540799, and NCT02510742, <https://clinicaltrials.gov>) with electrical stimulation of SPG in migraine patients might shed light into our understanding on the role of such procedures in treatment of migraine.

Current data is insufficient³ and more clinical studies are needed to understand the efficacy, tolerability, convenience, and long-term effect of SPG stimulation in the acute treatment of migraine. Moreover, molecular and imaging studies following SPG stimulation may shed light into the mechanism of its modulation of pain.

TTRANSCUTANEOUS ELECTRICAL STIMULATION OF SUPRAORBITAL NERVE (TESoSN)

Transcutaneous electrical stimulation of peripheral nerves in human has long been performed for various pain syndromes that could not be treated otherwise and the outcomes were satisfac-

tory.^{66,67}

These non-invasive impulse generator devices are placed on the skin close to the nerves and they transmit the electrical impulses transcutaneously through electrodes to the nerves.

A recent study using transcutaneous electrical stimulation of supraorbital nerve (TESoSN) for 8 weeks in 12 patients suffering from depression and post-traumatic stress disorder (PTSD) in an out-patient open trial resulted in significant improvement of the symptoms.⁶⁸ Available evidence shows some effectiveness of TESOsn in treatment of migraine.⁶⁹

Using a new stimulator called “Cefaly” (STX-Med, Herstal, Belgium), the supraorbital nerve branch of the trigeminal nerve was stimulated in a double-blinded, randomized, sham-controlled trial in 67 patients for the prevention of migraine in 5 Belgian tertiary headache clinics. The Cefaly headband is placed on the skin close to the supraorbital and supratrochlear branches of the ophthalmic nerve in the forehead and transmits the electrical impulses transcutaneously through a self-adhesive electrode to the nerves.^{70,71} Cefaly device has FDA approval.⁷¹ The stimulator was used daily for 20 min for 3 months. Results showed that the mean migraine days decreased significantly from 6.94 to 4.88 in the verum stimulated group while there was almost no difference in the sham stimulated group.⁷⁰ Primary outcome measures in that study was a change in monthly migraine days and 50% responder rate. Accordingly, the 50% responder rate was significantly higher (38.1%) in verum stimulated *versus* sham stimulated group (12.1%). Moreover, TESOsn reduced the attack frequency and total headache day but not the severity of the headache.⁷⁰ PET studies show that Cefaly increases the activity of limbic system including orbitofrontal and anterior cingulate cortices.⁷¹

Moreover, a recent study in 24 patients with low frequency migraine attack, a brief period of high frequency TESOsn improved multiple migraine severity parameters.⁷²

The safety and tolerability of TESOsn using Cefaly[®] device was studied in a large group (2313 headache sufferers) in general population who rented the device through internet for a 40-day trial period) and was found to be safe and well-tolerated by many people (although it did not help some people and they returned the device).⁷³

External trigeminal nerve stimulation in episodic migraine was also effective for at least 3 weeks but more studies with control group were suggested for better conclusion.⁷⁴

It appears TESOsn as a non-invasive approach has some moderate effects in the acute and preventive treatment of migraine but more clinical studies will shed lights in the efficacy of the method. One set back with the current technology might be its continuous its daily use for several minutes continued for

several months to alleviate some of the migraine symptoms.

ELECTRICAL STIMULATION OF VAGUS NERVE

Electrical stimulation of vagus nerve has been used to treat intractable epileptic seizures not responding to medication or surgery but there is no clear mechanism for the regulatory effect of vagus nerve stimulation (VNS) in relieving the symptoms.^{75,76}

Blood oxygenation level changes by VNS since it activates (or increase blood flow to) several cortical and subcortical structures.⁷⁷ Such changes are seen in different thalamic nuclei insular gyrus, postcentral gyrus, parts of temporal and occipital gyri and basal ganglia using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) studies in human.⁷⁸⁻⁸⁰ Brain blood flow increased in rostral and dorsal-central medulla, right postcentral gyrus, bilateral thalami and hypothalami, insular cortices and lower cerebellum upon left cervical VNS in partial epileptic patients while blood flow decreased bilaterally in hippocampus, amygdala and posterior cingulate gyri.⁷⁹

VNS in a few epileptic patients who were also suffering from migraine resulted in improvement of headache.⁸¹ VNS significantly improved the symptoms in 5 patients with chronic refractory migraine or cluster headache⁸² or in 4 adult female patients with drug-refractory chronic migraine⁸³ or in 13 patients with refractory epilepsy and migraine.⁸⁴

Nevertheless, a small study shows that low intensity VNS in epileptic patients decreased the thermal pain threshold in human subjects.⁸⁵

Some vagal afferent nerve fibers terminate in the trigeminal nucleus and animal studies show that electrical stimulation of vagus nerve modulates trigeminovascular nociception (see the discussion please). Both invasive and non-invasive VNS has recently been shown to inhibit cortical spreading depression in rat.⁸⁶

The VNS was delivered on 27 migraine patients with and without aura in an open-label, single arm, multiple attack pilot study and their results indicate the efficacy and tolerability of VNS in episodic migraine patients.⁸⁷

Up to 4 migraine attacks were treated in that study by VNS with two 90-sec dose at 15-min intervals that were delivered to the right vagus nerve (cervical branch) within a 6-week time period. Patients were allowed to self-treat at moderate or severe pain or following 20-min of a mild pain. The pain was aborted at 2 hours in 22% of patients with moderate or severe attacks at baseline.⁸⁷

Another more recent open-label, single-arm, multi-center study used VNS on 36 patients with chronic migraine and 14 suffering from high frequency episodic migraine (HFEM).

Patients self-treated up to 3 consecutive mild or moderate migraine attacks occurring in 2-week period by delivery of two 120-second doses on VNS at 3-min intervals to the right vagal nerve (cervical branch). They found that 56.3% of the patients had pain reduction ($\geq 50\%$ reduction in visual analog scale "VAS" score) at 1 hour and 64.6% at 2 hour. Of these patients, 35.4% and 39.6% reached a pain-free (VAS:0) situation at 1 and 2 hours respectively. The pain-relief rate was 38.2% and 51.1% at 1 and 2 hour respectively when all attacks (N=131) were considered and pain-free rates in latter cases were approximately half of the corresponding percentages, indicating that the non-invasive VNS is an effective method for acute treatment of chronic migraine or HFCM.⁸⁸

Another trial, a monocentric, randomized, controlled, double-blind study in 40 patients with chronic migraine also shows that electrical stimulation of the auricular branch of the vagus nerve by means of a battery driven handheld stimulator to the sensory areas of left ear at 1 Hz for 4 hours per day for 3 months has significantly reduced the pain days ($\geq 50\%$ reduction in headache days) and improved the headache impact test and disability assessment test.⁸⁹

Non-invasive vagal nerve stimulation (nVNS) in 20 patients with treatment-refractory migraine has also been shown to be effective in the prevention and treatment of episodic and chronic migraine patients with associated sleep disturbances.⁹⁰ In that 3-month open-label, prospective observational study, 20 patients with treatment-refractory migraine were treated twice daily with nVNS prophylactically at pre-specified times and acutely as the adjunctive therapy for migraine attacks. Results show significant reduction in frequency, intensity, and duration of pain and improvements in migraine associated disability, depression and quality of sleep in treatment-refractory migraine patients.⁹⁰

The most recent pilot prospective, multicenter, double-blind, sham-controlled study, the EVENT study,⁹¹ shows also that nVNS is well tolerated and safe but did not significantly change the headache days in chronic migraine patients who had >15 headache days per month. Fifty nine patients took part in this study, 30 patients with nVNS and 29 had sham-treatment. Patients had a 1 month baseline phase and were randomized subsequently to nVNS or sham-treatment for 2 months before receiving open-label nVNS. Mean reduction in the number of headache days was 1.4 in the nVNS versus 0.2 day in the sham-treatment group and the difference was not significant but there was a trend $p=0.56$. The study concluded that consistent use of nVNS as a prophylactic treatment of chronic migraine can reduce the headache days but larger sham-controlled studies are needed.⁹¹

The nVNS has also been effective in prophylactic treatment of cluster headache in PREVA group study. This prospective, open-label, randomized study worked on 48 patients who received adjunctive nVNS plus standard of care (SoC) and 49

control patients only with the SoC alone. The duration and plan of the study comprised of 2-weeks baseline phase followed by 4-weeks randomized phase (nVNS plus SoC *versus* control group who received only SoC alone) followed by 4-weeks extension phase (nVNS plus SoC). Their results show that the $\geq 50\%$ response rate was higher (40%) in the nVNS plus SoC group compared to 8.3% in the SoC alone treated control group.⁹²

There are evidences that electrical stimulation of the nerves leads to the release of neurotransmitters or neuromodulators and vasoactive substances from their peripheral and central nerve endings affecting the vascular permeability or tissue inflammatory molecules peripherally and neurotransmission in the CNS.⁹³⁻⁹⁵ Electrical stimulation of the vagus nerve seems to decrease the severity of rheumatoid arthritis perhaps by inhibition of cytokine production.⁹⁶

Overall, nVNS seems promising in the acute and preventive treatment of migraine and is suggested to be continued in clinical trials³ to gather more information about its effectiveness in the treatment of migraine headaches and to understand the mechanism(s) of its effectiveness in trigeminocervical pain. In addition, as discussed above, blood oxygenation level and metabolic activities of a number of brain regions increase or decrease following VNS.⁷⁷⁻⁷⁹ Therefore, more basic research in VNS may add more knowledge to our current understanding of the brain central pain modulatory centers.

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a method that has been used to activate the motor cortex and study the facial motor responses⁹⁷ or elsewhere in the body⁹⁸ but it also seems to alleviate the pain of migraine patient with aura.⁹⁹

Transcranial stimulation is based on electromagnetic technology. A pulse of current passes through a coil that is located in a portable device which can be placed on the individual's head (i.e. in the occipital region) for a short time and when turned on, it depolarizes neurons in the target area.¹⁰⁰

A randomized, double-blind, parallel-group, two phase, sham-controlled study in 18 centers in the United States investigated the pain relief in 267 adults suffering from migraine with aura, of which 66 patients were dropped in phase one. The remaining 201 patients were randomly chosen to have the single-pulse transcranial magnetic stimulation (sTMS, n=102) or sham-stimulation (n=99).¹⁰¹ The patients were informed to treat up to 3 attacks over 3 months when experience aura. Out of 201 patients, 37 who didn't treat a migraine attack were excluded and the rest were divided equally into the sTMS or sham stimulated groups (n=82 for each group). The pain-free response after 2 hours was 39% in the sTMS group compared to 22% in the sham stimulated group. Pain free status at 24 hours and 48 hours post-treatment was still significantly higher in the TMS group but other symptoms such as nausea, photophobia and phonopho-

bia were not changed, nor there were serious side effects in the sTMS or sham stimulated group. That study shows the effectiveness of single-pulse TMS in acute treatment of migraine with aura patients.¹⁰¹

A survey of 190 patients with episodic (n=59) and chronic (n=131) migraine with and without aura after 3 month following single-pulse TMS shows 62% of the patients reported pain relief and over 52%-55% had reduction of associated symptoms such as nausea, photophobia and phonophobia. After 3 month, the mean headache days in episodic migraine reduced from 12 to 9 days and for the chronic migraine patients from 24 to 16 days.¹⁰⁰

A recent study in rats and cats shows that single-pulse TMS is able to inhibit both mechanical and chemically-induced cortical spreading depression and reduced the firing of third-order neurons (thalamocortical) but not 2nd-order neurons of the trigeminocervical complex.¹⁰²

All together, these studies show the efficacy of single-pulse TMS in the non-pharmacological treatment of migraine but more studies on the aura symptoms and perhaps effect of TMS on cerebral blood flow might be helpful, however, the procedure seems to be safe and tolerable.¹⁰³

DISCUSSION

Migraine is one of the most prevalent neurological disorders that is characterized by headache, gastrointestinal problems and sensory dysfunction. Because of its multifactorial etiology, migraine is very difficult to treat. Migraine therapy is based on the acute and preventive treatments. There are several pharmacological and non-pharmacological treatments of migraine currently available in clinical practice. Many of the pharmacologic treatment of migraine have side effects and contraindications and with the insufficient efficacy and dissatisfaction they are often discontinued.^{71,104} Using medication such as triptans and NSAIDs may lead to chronic migraine.¹⁰⁵ A large-scale study based on US health insurance claims database during 2003-2005 on 4634 patients who started migraine prophylaxis with antidepressants, antiepileptic drugs, or beta-blockers shows that they were no longer taking these medications at 6 months.¹⁰⁶ Therefore, alternative and additional treatment options are necessary for the unmet treatment of migraine. This review was aimed to update us on the new advances in the treatment of migraine through neuromodulation. A number of clinical studies in recent years initiated the acute and preventive treatment of migraine specially the chronic medically intractable headaches using novel invasive and non-invasive neurostimulation of the peripheral and central nervous system.

The invasive devices are implanted subcutaneously or through other surgeries and are powered by implantable batteries or controlled wirelessly, while the non-invasive devices are applied on the skin close to the nerve and can be self-adminis-

tered by the patient as well.¹⁰⁷

The exact mechanism of pain relief by electrical stimulation of nerves is not known very well but it might be due to modulating the release of neurotransmitters including neuropeptides in the CNS and closing the gate of pain and also the brain areas involved in pain processing.^{50,51}

Other studies suggest a central control for pain following such stimulations as seen in VNS⁷⁸⁻⁸⁰ studies and ONS in cluster headache (CH) patients. Using metabolic neuroimaging by PET, several areas of brain of CH patients showed hypermetabolism.¹⁰⁸ Increased hypermetabolism seen by uptake of [18F] fluorodeoxyglucose (FDG) was detected on PET in the ipsilateral hypothalamus, midbrain, and ipsilateral lower pons of CH patients.¹⁰⁸ All hypermetabolic areas were normalized following ONS except the hypothalamus which was proposed to be possibly responsible for the autonomic attacks persistence despite pain relief.¹⁰⁸ In the responders of ONS in that study, the perigenual anterior cingulate cortex was hyperactive compared to non-responders, indicating the importance of this endogenous opioid system in the brain in modulating pain.¹⁰⁸

Moreover, ONS and transcutaneous electrical stimulation might relieve pain through neuro-modulatory effects in the limbic system and cortical pain control areas, see reference for review.⁷¹

Electrical stimulation of the greater occipital nerve was one of the invasive methods discussed in this review. Two major studies were mentioned: The ONSTIM feasibility study.⁵⁵ Occipital nerve stimulation (ONS) was delivered by means of a pulse generator device that was surgically implanted subcutaneously superficial to the fascia and muscle layer of the back of the neck at the C1 level.⁵⁵ Hundred and ten patients with chronic migraine participated in the ONSTIM feasibility study. Seventy five of them were the treated (adjustable stimulated) group. The number of 3-month responders with 50% or more reduction in the number of headache days per month was at 39% in the adjustable stimulated group compared to 6% in the preset (control) stimulated group.

The other large-scale study discussed in this review used ONS on 105 chronic migraine patients and 52 with sham-stimulation. That study showed only a significant difference in the percentage of patients who had 30% decrease in the mean daily visual analog scale scores by 12 weeks (pain reduction) following the stimulation.⁵⁶ The primary end point in that study was the difference in the percentage of responders that achieved $\geq 50\%$ reduction in mean daily visual analog scale scores by 12 weeks following the procedure.⁵⁶

These studies show the efficacy of ONS in treating some chronic migraine patients although the majority of the patients may not have fully benefited from the ONS. Some of the side effects such as paresthesia or infection, other surgery-relat-

ed complications, electrode migration, and battery depletion and replacement, and implant site pain can be seen in the invasive nerve stimulated patients.^{55,56,71} Nevertheless, more ONS studies on selected patients with more uniform results may be necessary for its recommendation³ which may also help finding more optimal procedural protocols and guidelines.

A number of reasons might contribute to the difference in the responses among patients. These may include the diversity in the etiology of migraine and the different trigger points compared to the level(s) of modulation. Usually these stimulations lead to neuronal modulation at the first central synapses in the spinal cord or trigeminal nucleus and may be confined to a small area in that level and higher CNS areas. If the trigger point for the migraine lies outside the peripheral and/or central territory of the occipital or other stimulated nerves, the modulatory effect of stimulation may not reach the trigger area of the central nervous system. Other reasons might be the peripheral and central sensitizations that may not be affected by such stimulations due to the involvement of multiple signaling molecules.¹⁰⁹ Although, procedural and technical errors or surgical complications in general can also contribute to different outcomes but these are usually recognized by the investigators conducting the study.

The other invasive method mentioned in this review was the electrical stimulation of the sphenopalatine ganglion (SPG) for the treatment of acute migraine.

The mechanisms of pain relief following SPG stimulation might possibly be due to interruption of postganglionic parasympathetic outflow and modulation of sensory processing in the caudal trigeminal nucleus.⁶⁰

In one study mentioned here electrical stimulation of SPG for ≤ 60 minutes in 10 patients with refractory migraine alleviated the pain in 50% of the patients.⁶⁵ Currently, there is insufficient data on the efficacy, long-term effect and side effects of SPG stimulation in the treatment of acute migraine. However, sphenopalatine ganglion and its innervation and function is extremely important and relevant for migraine and cluster headache studies and more research including the clinical trials mentioned above in this review will add more to our understanding of the pathomechanism of migraine.

Other neuromodulation/stimulation methods applied for the acute and preventive treatment of migraine with some shown efficacy that were discussed here include the non-invasive electrical stimulation procedures such as vagal nerve stimulation,⁸⁷⁻⁹² the transcutaneous electrical stimulation of supraorbital nerve (TESoSN) and single-pulse transcranial magnetic stimulation.

Some afferent vagal nerve fibers project to the brain stem trigeminal nucleus.¹¹⁰ The mechanism of pain relief following electrical stimulation of the vagus nerve might be due to

vagal afferent being able to modulate trigeminovascular pain in the brain stem. Continuous electrical stimulation of vagus nerve in rats modulates trigeminovascular nociception possibly due to decrease in neurotransmitters such as glutamate.¹¹¹ Electrical stimulation of cardiopulmonary vagal afferent in anesthetized rats modulates nociception in the trigeminal and trigeminothalamic neurons in response to painful orofacial stimulation.^{112,113} Therefore, electrical stimulation of the vagus nerve has some promising results and more clinical trials should add more to our current understanding of neurostimulation method in the treatment of migraine.

The TESoSN has some moderate effects in the acute and preventive treatment of migraine. One set back with the current technology might be the necessity for its continuous daily use for several minutes continued for several weeks or months to treat migraine.

Table 1 is a brief review of major studies (and their results) that used nerve stimulation to treat migraine in the last couple of years.

CONCLUSION

Although a number of medications are available for the acute and preventive treatment of migraine, neurostimulation techniques have also been used in the treatment of medically intractable headaches in clinical studies in recent years.

Their ability to influence brain network interactions is advancing their applicability.

Among these, electrical stimulation of greater occipital nerve or sphenopalatine ganglion are the invasive ones and the non-invasive procedures include the vagal nerve stimulation, the supraorbital nerve stimulation or the single-pulse transcranial magnetic stimulation.

These recent advances in the management of migraine show some degrees of success. Vagal nerve stimulation is promising and because it is also used in the treatment of other conditions such as epilepsy, advances in this field can help treatment of headaches and other disorders as well as understanding of the mechanism of pain relief. Occipital nerve stimulation results are diverse, and sphenopalatine ganglion stimulation studies are insufficient³ but are relevant and interesting in headache research. Therefore, more such neuromodulation/nerve stimulation studies with long-term follow up may be necessary to learn more about their tolerability, convenience, effectiveness and side effects in the acute and preventive treatment of migraine. In addition, these clinical studies will shed light into our understanding of pathomechanism of migraine.

Future direction and research in this field can greatly benefit from the guidelines and Consensus Statement of the

Neuromodulation procedure	Major studies done	Results
Occipital nerve stimulation (ONS)	<ul style="list-style-type: none"> - ONSTIM feasibility study: used ONS by means of subcutaneous implantation of a pulse generator device for preventive treatment of chronic migraine.⁵⁵ - 75 out of 110 eligible patients were assigned to treatment group.⁵⁵ - Another large-scale study used ONS to chronic migraine patients (105 patients with active stimulation and 52 with sham stimulation).⁵⁶ the criteria for responders were those patients that achieved $\geq 50\%$ reduction in mean daily visual analog scale scores by 12 weeks following the procedure.⁵⁶ -Another study used ONS on 53 patients with chronic migraine (CM) and some within this group suffering from other associated chronic headache phenotypes in addition to CM.⁵⁷ 	<ul style="list-style-type: none"> - The treated group (adjustable stimulation group) showed 39% 3-month responders but the control group (preset stimulation or medical management) had 6% and 0% 3-month responder rates.⁵⁵ - There was a significant difference in the percentage of patients that achieved 30% but not 50% pain reduction. There was also reduction of headache days and other associated symptoms in active stimulated group.⁵⁶ -After an average of 42 month follow up, there was a 45.3% response rate in the whole cohort defined as $>30\%$ reduction in moderate to severe headache days per month. The overall mean subjective patient estimate of improvement was 31.7%.⁵⁷
Pterygopalatine (Sphenopalatine) ganglion stimulation	<ul style="list-style-type: none"> - One clinical study used electrical stimulation of SPG for ≤ 60 minutes in 10 patients suffering from refractory migraine.⁶⁵ - A few other studies are in clinical trials at the moment. 	<ul style="list-style-type: none"> - The pain was alleviated in only half of the patients although the failure might have been due to technical problems.⁶⁵
Transcutaneous electrical stimulation of supraorbital nerve (TESoSN)	<ul style="list-style-type: none"> - One investigation in five Belgian tertiary headache clinics used TESoSN in 67 patients for the prevention of migraine. They used a new stimulator called "Cefaly" for 20 min/day for 3 months.⁷⁰ 	<ul style="list-style-type: none"> - Mean migraine days decreased significantly from 6.94 to 4.88 in the verum stimulated group but almost no difference in the sham stimulated group. The 50% responder rate was significantly higher (38.1%) in verum stimulated versus sham stimulated group (12.1%).⁷⁰
Non-invasive vagal nerve stimulation (nVNS)	<ul style="list-style-type: none"> - VNS was applied on 36 patients with chronic migraine and 14 suffering from high frequency episodic migraine (HFEM).⁸⁸ - 40 patients with chronic migraine had electrical stimulation of the auricular branch of the vagus nerve by means of a battery driven handheld stimulator to the sensory areas of left ear at 1 Hz for 4 hours per day for 3 months.⁸⁹ - EVENT study: 59 patients with chronic migraine took part in this study. 30 patients with nVNS and 29 had sham treatment. Patients had a one month baseline phase and were randomized subsequently to nVNS or sham treatment for 2 months before receiving open-label nVNS.⁹¹ - PREVA study: 48 patients in received adjunctive nVNS plus standard of care (SoC) and 49 control patients only with the SoC alone for prophylactic treatment of cluster headache.⁹² 	<ul style="list-style-type: none"> - 56.3% of the patients had pain reduction ($\geq 50\%$ reduction in visual analog scale "VAS" score) at 1 hour and 64.6% at 2 hour.⁸⁸ - Of these patients, 35.4% and 39.6% reached a pain-free (VAS: 0) state at 1 and 2 hours respectively.⁸⁸ -Pain days was significantly reduced ($\geq 50\%$ reduction in headache days)⁸⁹ - It improved the headache impact test and disability assessment test.⁸⁹ - Mean reduction in the number of headache days was 1.4 in the nVNS <i>versus</i> 0.2 day in the sham-treatment group and the difference was not significant.⁹¹ - The $\geq 50\%$ response rate was higher (40%) in the nVNS plus SoC group compared to 8.3% in the SoC alone treated control group.⁹²
Transcranial magnetic stimulation (TMS)	<ul style="list-style-type: none"> - One study with 2 groups of migraine patients with aura used stimulation (sTMS) n=82 on one group and sham stimulation on control group, n=82.¹⁰¹ - Another investigation studies 190 patients with episodic (n=59) and chronic (n=131) migraine with and without aura using single-pulse TMS.¹⁰⁰ 	<ul style="list-style-type: none"> - The pain-free response after 2 hours was 39% in the sTMS group compared to 22% control group.¹⁰¹ - Pain free status at 24 hours and 48 hours post-treatment was still significantly higher in the sTMS group.¹⁰¹ - After 3 month following TMS 62% had pain relief.¹⁰⁰ - 52%-55% had reduction of associated symptoms such as nausea, photophobia and phonophobia.¹⁰⁰ - Mean headache days in episodic migraine reduced from 12 to 9 days and for the chronic migraine patients from 24 to 16 days.¹⁰⁰

Table 1: A brief review of the major clinical studies done for the treatment of migraine using electrical stimulation of various peripheral nerves/neurons or cranial neurons.

2013 European Headache Federation for clinical use of neuro-modulation in headache.¹¹⁴

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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