Taylor & Francis
Taylor & Francis Group

Expert Review of Medical Devices

ISSN: 1743-4440 (Print) 1745-2422 (Online) Journal homepage: http://www.tandfonline.com/loi/ierd20

Neuromodulation in migraine: state of the art and perspectives

Delphine Magis

To cite this article: Delphine Magis (2015) Neuromodulation in migraine: state of the art and perspectives, Expert Review of Medical Devices, 12:3, 329-339

To link to this article: http://dx.doi.org/10.1586/17434440.2015.1005606

Published online: 29 Jan 2015.

EXPERT REVIEWS

Neuromodulation in migraine: state of the art and perspectives

Expert Rev. Med. Devices 12(3), 329–339 (2015)

Delphine Magis

Headache Research Unit,
University Department of Neurology
CHR Citadelle, Boulevard du 12ème de Ligne 1, 4000 Liège, Belgium
Tel.: +32 2307 811
Fax: +32 4 2256 451
dmagis@chu.ulg.ac.be

Migraine is a highly prevalent and disabling disease. The drugs prescribed for migraine prophylaxis can have intolerable side effects or can be ineffective. Neuromodulation techniques are increasingly used in neurology. Transcutaneous supraorbital nerve stimulation is effective in episodic migraine prevention, whereas vagus nerve stimulation provides interesting results in acute migraine therapy. Transcranial stimulation techniques gave variable, and sometimes contradictory, results. The visual cortex is the target of choice in migraine: studies in migraine prevention and aura acute treatment are encouraging. These noninvasive therapies appear safe with a low rate of side effects. Available studies of invasive occipital nerve stimulation in chronic migraine gave modest results; but invasive occipital nerve stimulation offers a new hope to highly disabled patients who failed to respond to any other treatment. In the future, neuromodulation will probably take an increasing place in migraine treatment, as add-on therapy or alternative to medications, especially because of its attractive safety profile.

KEYWORDS: direct current stimulation • magnetic stimulation • migraine • neuromodulation • occipital nerve • peripheral nerve • supraorbital nerve • treatment

Migraine affects about 14.7% of the general population and is among the most prevalent disabling diseases according to the Global Burden of Disease Study 2010 [1]. Migraine is a primary headache disorder, that is, a headache without any underlying identifiable structural or psychiatric cause, and is characterized by recurrent headache attacks (at least five), lasting 4–72 h (untreated or unsuccessfully treated). The pain has at least two of the four following characteristics: unilateral location, pulsating quality, moderate or severe intensity and aggravation by/causing avoidance of routine physical activity; and is associated with either digestive signs (nausea and/or vomiting) or sensoriphobia (photophobia and phonophobia), as defined in the International Classification of Headache Disorders (ICHD)-3 beta classification [2]. According to the absence or presence of transient focal neurological symptoms (visual, sensory, etc.) preceding or sometimes accompanying the headache, migraine will be classified as 'without' or 'with' aura (ICHD-3 1.1 and 1.2 [2]). In opposition with the *episodic* form of migraine, when headache occurs at least 15 days a month for more than 3 months, and 8 of these headache days fulfill the criteria of migraine mentioned above, then the patient has *chronic* migraine (ICHD-3 1.3 [2]). The overuse of acute medications to treat the pain is the most common cause of chronic migraine headache (medication overuse headache, ICHD-3 8.2 [2]), and, main studies taken together, about the half of patients with medication overuse headache reverse to the episodic form when an acute drug withdrawal is performed [3].

People experiencing frequent attacks of episodic migraine or chronic migraine are the most disabled patients and need a prophylactic treatment, to reduce their attack frequency. Available preventive drugs are unfortunately not migraine specific and were actually designed to treat other diseases. The main categories are β-blockers, calcium channel blockers, antidepressants and antiepileptics. These medications can have intolerable side effects and in many patients several attempts with different drugs are often needed to find an effective therapy, so that the discontinuation rate

 10.1586/17434440.2015.1005606 ISSN 1743-4440

Figure 1. Transcutaneous supraorbital nerve stimulator Cefaly® by Cefaly Technology®.

of these preventive medications is high [4]. There is thus a need for treatments with fewer side effects and similar efficacy or for migraine-specific prophylaxis.

In the relative absence of new emerging prophylactic drugs, neuromodulation treatments targeting peripheral nerves or the brain itself have been developed to treat migraine and offer an attractive alternative to medications, besides nonpharmacological approaches such as behavioral therapy [5]. The International Neuromodulation Society defines neuromodulation as 'the alteration of nerve activity through the delivery of electrical stimulation or chemical agents to targeted sites of the body' [6]. The aim of neuromodulation is to restore function or relieve symptoms by modulating an abnormal neural pathway behavior caused by the disease process [6]. In migraine, neuromodulation approaches range from noninvasive techniques, such as transcutaneous supraorbital nerve stimulation to surgically implanted devices like occipital nerve stimulation.

This special report will review the latest literature available on neuromodulation in migraine (July 2014) and give a critical view on the strengths and limitations of these techniques.

Figure 2. Transcutaneous vagus nerve stimulator Gammacore® by Electrocore®.

Acting on peripheral nerves to prevent migraine

Peripheral nerve stimulation (PNS), that is, electrical stimulation of a peripheral nerve, is a well-known way to treat pain within this nerve territory. In the 1st century AD, the roman physician Scribonius Largus already wrote that applying an electric fish on the painful skull area during a head pain was able to relieve patients [7]. The analgesic effects of PNS, in general, have been attributed to several mechanisms: activation of afferent Aβ fibers, gate control in the spinal cord and descending supraspinal control from the rostroventromedial medulla or the periaqueductal gray [8,9]. PNS is widely used in chronic pain syndromes, such as neuropathic pain or the complex regional pain syndrome [10]. Along the same line, PNS was performed to treat headaches, first occipital neuralgia [11], and more recently migraine (and other primary headaches such as cluster headache).

PNS can be applied noninvasively through the skin or invasively with devices surgically implanted into the body. The choice will be mainly conditioned by the patient profile (headache history and aspirations) and by the device availability. It appears sound to start with noninvasive PNS devices, even in the most disabled patients like those with drug-refractory chronic migraine, despite lack of studies in that subpopulation. This therapeutic approach was recently introduced in headache societies' guidelines [5,12].

Noninvasive PNS

The analgesic effects of transcutaneous electrical nerve stimulation have been known for a long time. The benefits of transcutaneous electrical nerve stimulation in headache management had been suggested previously [13], but properly designed trials were lacking [14].

Till date, two noninvasive PNS techniques have been studied in migraine prophylaxis: transcutaneous supraorbital nerve stimulation (tSNS, Figure 1) and transcutaneous vagus nerve stimulation (tVNS, Figure 2). The efficacy of tSNS is demonstrated in two studies (one randomized controlled trial [RCT]) [15,16], whereas only one case report in abstract form is available for tVNS in migraine *prophylaxis* [17].

The effectiveness of a portable tSNS device in the prevention of episodic migraine was recently evaluated in a randomized, double-blind, sham-controlled trial [15]. Sixty-seven migraineurs with at least two attacks per month underwent a preventive treatment with effective or sham tSNS. After 3 months of daily 20-min sessions, the mean number of migraine days decreased significantly in the tSNS (6.94 vs 4.88; $p < 0.05$), but not in the sham group (6.54 vs 6.22 p = ns). The 50% responder rate was significantly greater in the tSNS (38.1%) than in the sham group (12.1%, $p < 0.05$). Migraine attack frequency and acute drug intake were also significantly reduced in the verum but not in the sham group. The safety of this tSNS device and the overall patient satisfaction were recently assessed in a larger population of 2313 'allcoming' migraineurs who rented the neurostimulator in countries where it is directly available on the internet without any medical prescription [16]. After a testing

period of 58.2 days on average, a majority (53.7%) of patients was satisfied and kept the tSNS device as migraine treatment. Among the unsatisfied patients, a device analysis showed a poor compliance, as on average these patients used tSNS less than 50% of the recommended time, and 4.46% did not even switch it on. Ninety-nine subjects out of the 2313 (4.3%) reported one or more adverse event(s). Although none of them was serious, about half of these subjects (i.e., 2%) stopped tSNS preventive therapy because of this adverse effect. Besides very rare skin allergies under the forehead electrode (0.09%), the most frequent adverse event was intolerance to forehead paresthesias that were perceived as painful burning sensations. This is of importance because paresthesias are 'typical' sensations linked to electrical stimulations of a peripheral nerve and explain the difficulty in blinding PNS studies. Moreover, a small proportion of the general population does not tolerate the sensations induced by cutaneous electrical stimuli even at low intensities. This intolerance may be more pronounced in migraine sufferers because of the cutaneous allodynia that may persist in some of them between attacks [18]. The mode of action of tSNS in migraine prevention is currently unknown, but is likely to involve slow neuromodulatory processes because its positive effects significantly differed from placebo after 2 months of daily therapy and became maximal after 3 months [15]. Because tSNS has not been studied in the prevention of other types of cephalic pain syndromes, its migraine-specific action cannot be affirmed, and a nonspecific analgesic effect cannot be ruled out (see below invasive occipital nerve stimulation [iONS]).

The efficacy of *invasive* vagus nerve stimulation (iVNS) in migraine prevention had been suggested by several case reports of patients who were initially treated for epilepsy (summarized in [18]). In a retrospective study lead by Lenaerts, 8 of 10 patients with migraine had at least a 50% reduction in headache frequency 6 months after iVNS implantation compared with the 3-month baseline period [19]. The other surveys included a very small number of patients but reported overall a decrease of migraine frequency in about 50% of patients treated with iVNS [18]. Hence, new devices thought to stimulate the vagus nerve transcutaneously (tVNS) in its cervical portion or its inner terminal branch in the external acoustic canal have recently been developed and are under evaluation in several types of diseases. Their efficacy as preventive treatment of primary headaches, among them migraine, is being studied as well. Preliminary open results on a mixed headache population showed that these tVNS devices could help some migraine patients [17], but well-designed studies in the selected migraine population are needed. Conversely, an open trial using tVNS in migraine *acute* treatment has just been published (see below, [20]). The mode of action of VNS is obscure. It is believed to modulate several cortical and subcortical structures, among them areas involved in nociception.

Finally, portable devices able to stimulate the great transcutaneous occipital nerve stimulation (tONS, Figure 3) are available on the market in several European countries, but for now their efficacy in migraine prevention has never been studied.

Figure 3. Transcutaneous occipital nerve stimulator by Cefaly Technology®.

Invasive PNS

Invasive PNS has been mainly performed in the most disabled patients with migraine, that is, patients having chronic migraine, because most techniques imply several surgical procedures (electrodes, batteries, etc.). Even if other invasive PNS techniques should be evaluated in migraine prevention, to date, clinical trials are only available for invasive (subcutaneous) great iONS, used alone (Figure 4) or in combination with invasive supraorbital nerve stimulation (iSNS).

The initial rationale for using iONS in migraine comes not only from findings in animals showing the convergence of cervical, somatic and dural (trigeminovascular) afferents on second-order nociceptors in the trigeminocervical complex [21,22] but also to some extent from the efficacy of great occipital nerve steroid injections in the prevention of various primary headaches [23,24]. However, it appears that the value of prior great occipital nerve injection to predict iONS effectiveness is unknown [25].

Besides small and/or heterogeneous open studies, three short-term (3 months each) randomized controlled trials have been published about migraine prevention [26–28], among them one in abstract form only [26]. Preliminary findings of the ONSTIM study ([27], 66 patients) demonstrated a reduction of at least 50% in headache frequency or a fall of 3 points on the intensity scale in 39% of chronic migraineurs treated with active iONS during 12 weeks, whereas no improvement was seen in sham or 'noneffectively' stimulated groups. In the sham-controlled PRISM study [26], iONS did not produce any significant reduction of headache days in the 125 patients with drug-resistant migraine who completed the 12-week assessment period. However, this cohort was heterogeneous because patients experienced migraine with or without aura, chronic migraine, and/or medication overuse headache. The latter could explain a less favorable outcome. Finally, Silberstein *et al.* [28] performed the last large study involving 157 patients with chronic migraine and randomly assigned to active iONS or to sham stimulation, again during a 3-month period. No difference was found between the two groups as far as the primary outcome (that is, the 50% responders in mean daily visual analog scale scores) was concerned. However, there was a significant difference in the percentage of patients who achieved a

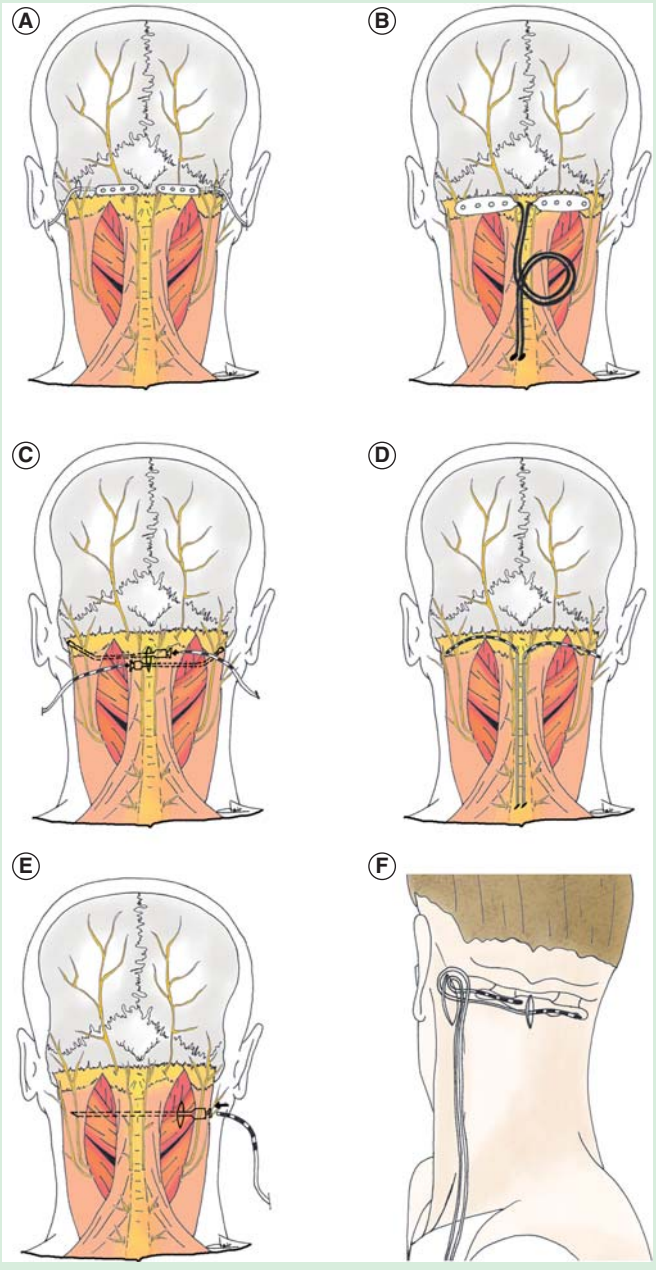

Figure 4. Different techniques of invasive occipital nerve stimulation.
Courtesy of Dr D. Fontaine, Dept. of Neurosurgery, CHU of Nice, France.

30% reduction in visual analog scale scores ($p < 0.05$). The decrease in the number of headache days was higher in the active group when compared with that in the control group ($p < 0.01$), as well as the decrease of migraine-related disability score ($p < 0.01$). The long-term follow-up of these patients was presented in the last International Headache Congress in Boston (June 2013), but has not been extensively published yet [29]. After the 3-month randomized phase, the patients entered an open-label phase of 40 weeks. Headache days were significantly reduced by 6.7 days for the intention-to-treat and 7.7 days for the intractable chronic migraine ($p < 0.01$) populations, as well as disability scores. Patients' self-assessed relief and satisfaction improved.

The most frequent complications after iONS are electrode migration (0–100% according to the studies [18]) and battery depletion because of high stimulation intensities, both requiring another surgical intervention [18]. Despite the increasing use of rechargeable batteries, a new surgery can probably not be avoided in the middle or long term [18]. Another complication is the early or late iONS device infection that sometimes implies to replace all the (costly) material. The risk of infection increases with the number of local surgeries, for example, to replace the empty batteries (personal observation). Finally, a well-conducted detoxification has to be performed in patients experiencing chronic migraine with medication overuse before considering iONS because drug overuse seems to be associated with a less favorable outcome under iONS [30].

The mechanism of action of iONS in chronic migraine is likely to be nondisease specific. Besides the probable modulation of the functional connexions described above in animal models [21,22], iONS seems to exert a nonspecific effect on supraspinal pain control systems. Two PET scan studies performed before and after successful treatment of two distinct primary headaches with iONS (i.e., chronic migraine [31] and chronic cluster headache [32]) demonstrated metabolic changes in the formerly called 'pain matrix' but not in central nervous system areas thought to play a pivotal role in the pathophysiology of these primary diseases.

Reed and colleagues reported the outcome of patients treated with a combination of iONS and iSNS [33,34]. In a recent communication [34], they retrospectively studied 44 patients with chronic migraine treated with iONS–iSNS (mean follow-up, 13 months). The frequency of severe headaches decreased by 81% and half of the patients had nearly complete disappearance of headaches. The complete results have not been published yet. The authors highlighted the therapeutic advantage of combined iONS–iSNS over iONS alone [33].

The few results available with iVNS have been cited above (see tVNS).

The sphenopalatine ganglion (SPG) is not a peripheral 'nerve' *per se* but an extracranial autonomic structure lying in the pterygopalatine fossa, which has connections with the trigeminovascular system [35]. The SPG was thus previously targeted by various lesional procedures to alleviate pain in several refractory primary headaches subtypes [18], but these techniques were not without risks, and one of the main complications was the occurrence of permanent neuropathic pain. A new device able to stimulate the SPG was recently developed, using a small microstimulator implanted surgically in the pterygopalatine fossa and activated through the cheek by a remote controller invasive sphenopalatine ganglion stimulation (iSPGS). A RCT using this iSPGS device was performed in another primary headache than migraine, that is, refractory chronic cluster headache [36], and even if the main objective of the study was to

treat the attacks, 36% of the patients (i.e., 10 out of 28) had a significant reduction of headache frequency, leaving room for a preventive therapy by iSPGS in this indication. RCT of refractory chronic migraine prevention with iSPGS are of interest because some of these patients may have side-locked attacks with autonomic symptoms, such as lacrimation, nasal congestion and conjunctival injection, all parasympathetic manifestations [35]. A recent review concluded that iSPGS could be effective in migraine via two mechanisms of action, first by interrupting the postganglionic parasympathetic outflow and inhibiting the pain and cephalic autonomic symptoms, and second by modulating the sensory processing in the trigeminal nucleus caudalis [35].

Modulating the brain activity to prevent migraine

Two main approaches are currently being evaluated with interest in migraine prevention: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Both are noninvasive and relatively safe ways to modulate the excitability of the underlying cerebral cortex. Invasive brain neurostimulation has never been performed in migraine up to now because the choice of the brain area to stimulate remains elusive in this multifaceted disease and because this technique is not without risks (a lethal hemorrhage has been described in cluster headache [37]).

Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has been used in clinical neurophysiology for several decades. It modulates the excitability of the underlying cerebral cortex in the way of a depolarization or hyperpolarization, using a rapidly changing magnetic field delivered by a coil applied at the scalp surface. TMS can be delivered as one single pulse (sTMS) or by trains of repeated stimulations (rTMS). rTMS induces longer lasting changes within the underlying cortex, overall low-stimulation frequencies (i.e., 1 Hz) are thought to have an inhibitory effect [38], whereas high frequencies (≥10 Hz) are considered as excitatory [39]. It was previously demonstrated that rTMS was able to modify the excitability of the visual cortex in healthy volunteers and patients with migraine durably and balance the electrophysiological abnormalities usually found in migraineurs within that brain area [40,41]. Its clinical application to migraine prevention was thus worthwhile, but few studies are available, probably because of the lack of accessibility of the stimulation device that is not transportable, very expensive and not user-friendly. Therefore, patients have to come to the clinic to receive their treatment with rTMS, which is hardly feasible in the middle or long term.

Up to now, three brain areas have been targeted in the studies of migraine prevention using rTMS: the left dorsolateral prefrontal cortex, the motor cortex and the visual cortex.

Brighina and colleagues [42] used excitatory rTMS (20 Hz) over LDLPFC, a brain area that is known to exert a pain-reducing top-down control, based on the assumption that the latter would be hypoactive in chronic migraine such as in other chronic pain conditions. Eleven chronic migraineurs received 12 sessions of high-frequency rTMS or sham (placebo) stimulation. At the end of the treatment, attack frequency, headache index and use of acute medications were reduced, and this effect lasted up to 2 months [42]. There was no significant improvement in the five patients receiving the sham stimulation. These positive results were not confirmed by a very recent trial, where 18 patients with chronic migraine were also treated with high-frequency (10 Hz) rTMS over the LDLPFC, which turned out to be less effective than sham stimulation [43]. Hence, larger studies are necessary before concluding that LDLPFC stimulation is effective in preventing chronic migraine, and other brain areas could be more interesting to target in migraine prevention. The motor cortex is a well-known area of neuromodulation in the treatment of refractory neuropathic pain. In migraine prophylaxis, the stimulation of the motor cortex with excitatory rTMS was superior to sham stimulation according to a recently study published by Misra *et al.* in 100 patients [44]. Even if the number of patients enrolled in the latter study is impressive, it has many shortcomings because sham stimulation induced a (very) significant improvement as well, although lower than rTMS itself, and also because all migraine phenotypes were included and received the same stimulation paradigm (episodic migraine, chronic migraine with and without analgesic overuse). Working under the hypothesis that in episodic migraine, the brain is hyperexcitable between attacks, Teepker *et al.* applied inhibitory rTMS (1 Hz) over the vertex in migraine prevention, postulating that this treatment could return this hyperexcitability to normal [45]. This trial was also negative because the number of migraine attacks and days did not differ significantly between inhibitory rTMS and sham stimulation. The negativity of this study could be attributed to an incorrect rationale, because in episodic migraine, most electrophysiological trials demonstrate that the cortical preactivation level and the habituation of sensory cortices to repeated stimulations are reduced [46]. This is not the case in chronic migraine, where the studies suggest heightened cortical preactivation levels [46], such as in a 'never ending attack' [47]. It is thus likely that the therapeutic effect of rTMS in migraine will not be linear and will depend on the baseline activation level of the underlying cortex and in consequence the stimulation parameters will have to vary according to the migraine subtype. This hypothesis was recently tested in 16 chronic migraineurs who received inhibitory quadripulse (QP) rTMS over the visual cortex during a 4-week pilot trial in migraine prevention (two rTMS sessions/week as add-on therapy) [48]. Briefly, QP rTMS is a short stimulation paradigm that allows long-lasting cortical after-effects in a way of facilitation or inhibition [49]. A majority of patients improved significantly after inhibitory QP rTMS therapy, which could be attributed to a normalization of their heightened cortical preactivation level because of the inhibitory treatment. Monthly migraine days decreased on average from 22 before to 13 after QP rTMS (−41%, $p < 0.05$), and severe attacks were reduced by 25% ($p < 0.05$). The 50% responder rate was 38%, whereas the half of patients reversed from the chronic to the episodic

form of migraine. Acute medication intake was significantly decreased (−55.5%, $p < 0.05$). The clinical improvement remained stable for at least 1 month after the end of QP rTMS, with an average of 10.9 migraine days/month (−50.5% compared to baseline, $p < 0.05$) (86). There were no adverse events and, interestingly, medication overuse did not modify the response to QP rTMS therapy. A sham-controlled trial is now necessary to confirm these results and exclude a placebo effect.

Transcranial direct current stimulation

tDCS is a simple technique, which was already being used to treat neurological disorders in the 19th century but had a high rate of side effects (especially burns of the underlying soft tissues). Nowadays, it has become a secure brain neuromodulation technique if safety guidelines are respected and is increasingly used in various neurological disorders ranging from chronic pain to comas. tDCS uses weak currents to modify the resting membrane potential of brain cells, leading to focal modulation of cortical excitability. Similar to rTMS, two opposite effects can be obtained with tDCS: cathodal stimulation inhibits neuronal firing, whereas anodal stimulation increases it. In healthy volunteers, tDCS is able to modulate not only resting EEG and event-related potentials [50] but also functional connectivity of corticostriatal and thalamocortical circuits [51]. This is of particular interest in migraine because it is thought to be associated with thalamocortical dysrhythmia [52].

Few small tDCS studies are available in migraine (motor and visual cortices), but this number should increase in the future because tDCS devices are far less expensive than rTMS, can be transported and used by the patient after some explanations. Side effects of tDCS are all mild and reversible, and mainly consist of a transient tingling sensation at the site of stimulation.

DaSilva *et al.* performed a sham-controlled trial in 13 patients, using anodal (i.e., excitatory) tDCS applied over the primary motor cortex for chronic migraine prevention [53]. They noticed a delayed positive effect on pain intensity and duration (120 days after stimulation) in patients treated with tDCS and not with sham stimulation, which was attributed to slow modulation of cortical and subcortical pain-related structures. A computational modeling analysis showed that significant electric fields were generated, not only in targeted cortical regions but also in the insula, cingulate cortex, thalamus and brainstem regions [53]. The therapeutic effect of inhibitory (cathodal) tDCS over the primary visual cortex in episodic migraine prevention was studied in a 6-week RCT involving 26 patients (three sessions/week) [54]. An inhibitory stimulation paradigm was chosen based on the hypothesis that the cortex would be hyperexcitable between attacks. Migraine days, duration and intensity decreased significantly after tDCS, but this change did not differ from sham stimulation, except for intensity. In a proof-of-concept study based on electrophysiological abnormalities cited above (see rTMS, [46]), that is, using the opposite rationale, Vigano *et al.* [55] evaluated the preventive effect of an 8-week excitatory (anodal) tDCS therapy over the visual cortex in 10 episodic migraineurs (two sessions/week). Migraine attack frequency, migraine days, attack duration and acute medication intake significantly decreased during the treatment period compared with pretreatment baseline and this benefit persisted on average 4.8 weeks after the end of tDCS. Moreover, an electrophysiological assessment found that a single session of anodal tDCS over the visual cortex was able to increase habituation to repetitive visual stimuli in healthy volunteers and in episodic migraineurs, who on average lack habituation interictally. That anodal tDCS has a significant preventive effect on migraine suggests that the lower preactivation level of the visual cortex found in episodic migraine patients can be corrected by an activating neurostimulation [55]. Along the same line, following electrophysiological findings, inhibitory (cathodal) tDCS of the visual cortex was then applied in 20 chronic migraineurs, using a portable device that allowed a daily 20-min tDCS session during 8 weeks. The anode of the device was placed over the LDLPFC to activate antinociceptive top-down mechanisms. Total headache days decreased significantly within the second month of tDCS therapy. Severe migraine attacks were reduced by 43.7% ($p = 0.05$) and cumulative total headache hours by 30.2% ($p = 0.02$). The 50% responder rate for migraine days was 33.3%. A total of 72.2% of patients were very or moderately satisfied with the therapy. Medication overuse did not modify the treatment outcome.

Larger sham-controlled tDCS trials targeting the visual cortex (where the electrophysiological abnormalities seem more consistent), and using these neuromodulation paradigms (i.e., anodal tDCS in episodic and cathodal tDCS in chronic migraine), delivered by portable devices should be of highest interest in the future.

Is there a place for neuromodulation in migraine acute treatment?

The only available study using PNS *per se* to treat the attacks of migraine is an open trial using tVNS with a portable device [20]. In this very recent study involving 27 patients, the pain-free rate at 2 h was 22% for all treated attacks with a moderate or severe headache at baseline. Mild adverse events were reported by 13 patients (48%), the more common were neck twitching, raspy voice and redness at the site of tVNS. Again, a sham-controlled trial is necessary and the improvement rates are rather low, but this trial highlights that tVNS could help some patients with migraine.

A small proof-of-concept study used percutaneous iSPGS in patients with 'intractable' migraine pain [56]. With this invasive technique where a removable electrode is inserted through the skin to stimulate the SPG via an infrazygomatic transcoronoid approach directly, the migraine pain could be suppressed (2) or decreased (3) in 5 of the 10 stimulated patients.

Regarding the place of brain stimulation in migraine attack treatment, a RCT was performed in 164 migraineurs with aura using a portable TMS device delivering two single magnetic pulses at 30-second interval over the visual cortex, within the first hour of aura onset [57]. Pain-free response rates at 2 h were 39% for TMS and 22% for the sham device ($p < 0.05$).

Although significant, the overall therapeutic gain was 17% only. Sustained pain-free rates at 24 and 48 h were in favor of TMS. The eligible population of this study had between two and eight migraine with aura episodes per month; therefore, it is not clearly stated whether some patients met the criteria for chronic migraine [2].

Finally, the effect of tDCS on migraine pain was evaluated in a sham-controlled trial involving 62 patients suffering from chronic migraine. Because this trial is only available in abstract form, few data are described, and the polarity (anode/cathode) is unknown. Surprisingly, both tDCS and sham stimulation led to a 54.2% reduction in headache intensity, suggesting a non-specific placebo effect [58].

Expert commentary

Neuromodulation is taking an increasing place in the migraine therapeutic armamentarium, besides effective nonpharmacological approaches such as cognitive–behavioral therapy [5], and even if large placebo-controlled studies are often lacking, it offers a new hope to some highly disabled patients.

Peripheral neurostimulation does not appear migraine specific and is effective in other pain conditions. Because of its potential effects on central pain-modulating systems, PNS could be compared with an 'electrical analog' of some oral analgesic drugs, except that PNS involves slow neuromodulatory processes and usually takes time to be effective. Most available migraine studies using neuromodulation are thus dedicated to prevention. Interestingly, like in some analgesic therapies, especially with opioids, patients can slowly develop a tolerance to the neurostimulation, which will need either the modification of the stimulation parameters or a transient interruption of the treatment (see [59], and personal observation).

The neuromodulation of specific brain areas with rTMS or tDCS is based on the activation of a specific pain-control descending systems (like the left prefrontal cortex or the motor cortex stimulation) or has a rationale based on migraine pathophysiological studies and could thus be more disease specific, like the visual cortex stimulation.

On the basis of our clinical experience, we found that neuromodulation can be proposed to several types of patients in need of a preventive migraine treatment:

- Patients who did not improve with the main preventive drugs are considered as drug-refractory.
- Patients who do not want to take any migraine preventive drug for personal reasons, mainly the fear of harmful or irreversible side effects (weight gain, cognitive disturbances, etc.).
- Patients who have absolute or relative contraindications to the use of migraine preventive drugs, or having significant side effects with many of them.
- Finally, patients who are partly improved by their migraine preventive medication, to avoid an additional preventive drug (add-on therapy).

As far as the choice of the technique is concerned, *non-invasive* PNS, especially tSNS, may be proposed to a larger population of less disabled patients with migraine as single or add-on preventive migraine therapy, given that adverse events are rare, mild and fully reversible. Even if evidence is lacking, noninvasive PNS devices should be tried first in drug-refractory patients, before going to invasive techniques, as advised by several recent guidelines [5,12]. Controlled studies with tONS and tVNS devices are eagerly awaited. The first portable tDCS devices are mainly prototypes, which are only available in headache-specialized centers. Their results on episodic and chronic migraine prevention are promising. According to the outcome of controlled studies, these devices could be accessible to the general migraine population in the future. tSNS Cefaly® device has received the CE mark and the US FDA approval and can thus be rented and purchased in many European and American countries (sale price around 300€), whereas for the moment tVNS Gammacore® device can be purchased in Europe only (CE mark, price unknown).

The data on i*nvasive* neuromodulation reviewed above highlight that iONS could offer a valuable alternative or add-on therapy for patients with chronic migraine, but only after the failure of several preventive medications and of noninvasive nonpharmacological treatments. Before choosing surgery and besides the cost of the device (more than 10,000€), patients must be well informed and aware that their improvement may be moderate or absent, and that invasive PNS procedures are certainly not without risks (infection, battery depletion and electrode migration).

Overall, the results of neuromodulation in the management of the migraine attack appear modest compared with the outcome of patients treated with migraine-specific drugs such as triptans (see [60] for a complete meta-analysis), but like in prevention, neuromodulation could be proposed as alternative to drugs in patients who have contraindication(s) or intolerance to usual acute therapies or as add-on treatment in patients who only get minor relief after taking these drugs. The portable SpringTMS® device used to treat migraine with aura in the RCT cited above [57] is currently available for rent in the USA and the UK (£150/month).

Five-year view

With the conception of portable, easy-going neuromodulation devices that could be borrowed or bought for an 'acceptable' price, the industry will contribute to the dissemination of techniques that were previously offered to a small number of patients consulting headache-specialized clinical research centers. Portable neurostimulation devices such as tSNS, tVNS, tONS are already available in some European countries and in the USA, but RCT remain to be performed to assess tVNS and tONS effectiveness in migraine prevention. These devices will perhaps join the antimigraine armamentarium and will be used as nonpharmacological alternative or be part of the multimodal management of the disease, together with preventive drugs and behavioral therapy. Noninvasive neuromodulation will be performed before considering the patient as refractory and is now mentioned in the latest guidelines [5,12]. If

transcutaneous ONS turns out to demonstrate some usefulness, it could be required before going to invasive ONS.

Noninvasive peripheral neurostimulation is now widely studied in various fields of neurology but will probably show limitations in the future. In migraine, interesting targets were mainly the trigeminal, occipital and vagus nerves, for which portable neurostimulation devices are now available. If tONS and tVNS efficacies are confirmed as well, a collaboration between the neurologists and the industry will be necessary to optimize the existing devices (shape, parameters and performance) and evaluate the advantage of one technique over the other, or to combine them.

The therapeutic possibilities offered by brain neuromodulation with tDCS and TMS appear larger, but the heterogeneity of the migraine phenotype and the cycling character of the disease are a real challenge in the design of migraine therapeutic studies using these techniques. The stimulation of deeper brain areas might be difficult or impossible because of their distance from the skin (e.g., the thalamus or the cingulate gyrus) or would require stimulation intensities that are not compatible with the safety guidelines or even with the device itself. Without any physiological trials combining tDCS and rTMS with functional imaging and/or electrophysiology, it remains unclear what type of modulation occurs and in the absence of a functional biomarker (phosphenes, limb movement, etc.), whether the brain target gets really stimulated. Hence, it has been shown that an excitatory stimulation could become inhibitory in the long term, and that transcranial stimulation effects could differ between individuals [61] or vary according to the underlying synaptic activity [62]. Even if prototypes of portable tDCS devices were used in some recent studies, the need to combine this technique with a functional marker might decrease its accessibility, whereas rTMS use will still remain limited to small amounts of patients due to the cost and the size of the latest devices.

Acknowledgements

The author would like to thank D Fontaine from the Department of Neurosurgery, CHU de Nice, France, for providing the Figure 4 *on invasive occipital nerve stimulation.*

Financial & competing interests disclosure

The author is currently involved in clinical trials with: Electrocore USA, Cefaly-Technology, Medtronic USA, St Jude Medical but did not receive any personal sponsorship or grants from these industries that could lead to a conflict of interest. This work was supported by the European Union, EUROHEADPAIN project, FP7, n 602633. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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

Key issues

- In a significant proportion of individuals, available drugs used for migraine prevention have often disabling side effects or are not effective.
- Neuromodulation devices offer a new therapeutic alternative, besides other nonpharmacological approaches such as behavioral therapy, and are being increasingly studied in migraine prevention, and to some extent in migraine acute therapy.
- These devices can be proposed to several categories of patients with migraine: those who are drug-refractory, who do not want to take any drug or who have contraindications or side effects with usual drugs.
- Noninvasive neurostimulation treatments are generally well tolerated and have few side effects (4.3% for transcutaneous supraorbital nerve stimulation), and with the availability of portable user-friendly devices, will be soon part of the migraine therapeutic armamentarium.
- Randomized controlled trials are lacking for most devices and should be performed in the future.
- Transcutaneous supraorbital nerve stimulation has shown its effectiveness in episodic migraine prevention, whereas invasive occipital nerve stimulation can help some patients having chronic migraine.
- Invasive neurostimulation should only be considered in patients with refractory chronic migraine, after failure of noninvasive therapies and in the absence of medication overuse.
- The neuromodulation of peculiar brain areas with rTMS or tDCS could be more disease specific and offer the largest therapeutic possibilities, but these techniques have technical issues that will be a challenge for future studies.

References

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

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2163-96
2. International Headache Society. The international classification of headache disorders, 3rd Edition (beta version). Cephalalgia 2013;33(9):629-808
3. Kristoffersen ES, Lundqvist C. Medication-overuse headache: a review. J Pain Res 2014;7:367-78
4. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). Headache 2013;53(4):644-55

• **This review well highlights the issues due to the adverse events of migraine prophylactic drugs.**

5. Paemeleire K, Louis P, Magis D, et al. Diagnosis, pathophysiology and management of chronic migraine: a proposal of the Belgian Headache Society. Acta neurologica Belgica 2014. [Epub ahead of print]

• **This study provides a very clear decision tree of chronic migraine management, as well as a complete review of its pathophysiology.**

6. Welcome to the International Neuromodulation Society. (International Neuromodulation Society), 2013. Available from: http://www.neuromodulation.com/
7. Largii S. Ad Capitis Dolorem. 1st century BC
8. Melzack R, Wall PD. Pain mechanisms: a new theory. Science New York, N.Y 1965;150(3699):971-9
9. DeSantana JM, Da Silva LF, De Resende MA, Sluka KA. Transcutaneous electrical nerve stimulation at both high and low frequencies activates ventrolateral periaqueductal grey to decrease mechanical hyperalgesia in arthritic rats. Neuroscience 2009;163(4):1233-41

• **This interesting animal study demonstrates that peripheral nerve stimulation acts on brainstem pain-modulating structures.**

10. Cruccu G, Aziz TZ, Garcia-Larrea L, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol 2007;14(9):952-70
11. Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. Neuromodulation 1999;2:217-22
12. Martelletti P, Jensen RH, Antal A, et al. Neuromodulation of chronic headaches: position statement from the European Headache Federation. J Headache Pain 2013;14(1):86

• **This is the first consensus paper on neuromodulation and its place in headache management.**

13. Solomon S, Guglielmo KM. Treatment of headache by transcutaneous electrical stimulation. Headache 1985;25(1):12-15
14. Bronfort G, Nilsson N, Haas M, et al. Non-invasive physical treatments for chronic/recurrent headache. Cochrane Database Syst Rev 2004;3:CD001878
15. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology 2013;80(8):697-704

•• **The first randomized controlled trial (RCT) showing the efficacy of non-invasive peripheral nerve stimulation (here supraorbital nerve) in migraine prevention.**

16. Magis D, Sava S, d'Elia TS, et al. Safety and patients' satisfaction of transcutaneous Supraorbital NeuroStimulation (tSNS) with the Cefaly(R) device in headache treatment: a survey of 2,313 headache sufferers in the general population. J Headache Pain 2013; 14(1):95

• **A prospective registry involving more than 2000 users of non-invasive supraorbital nerve stimulation that mainly discloses the very low rate of adverse events and underlines the issue of adherence to treatment in non-responders.**

17. Magis D, Gerard P, Schoenen J. Transcutaneous vagus nerve stimulation (tVNS) for headache prophylaxis: initial experience. J Headache Pain 2013; 1(Suppl 1):198
18. Magis D, Schoenen J. Advances and challenges in neurostimulation for headaches. Lancet Neurol 2012;11:708-19
19. Lenaerts ME, Oommen KJ, Couch JR, Skaggs V. Can vagus nerve stimulation help migraine? Cephalalgia 2008;28(4):392-5
20. Goadsby P, Grosberg B, Mauskop A, et al. Effect of noninvasive vagus nerve stimulation on acute migraine: An open-label pilot study. Cephalalgia 2014; 34(12):986-93

•• **This very recent study shows the efficacy of non-invasive vagus nerve stimulation in the treatment of the migraine attack. Though modest, these results open the way for the possible use of transcutaneous vagus nerve stimulation in patients who have contraindications or do not respond to acute antimigraine drugs.**

21. Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. Brain 2002;125(Pt 7):1496-509
22. Bartsch T, Goadsby PJ. Increased responses in trigeminocervical nociceptive neurons to cervical input after stimulation of the dura mater. Brain 2003;126(Pt 8):1801-13
23. Ambrosini A, Vandenheede M, Rossi P, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 2005;118(1-2):92-6
24. Leroux E, Valade D, Taifas I, et al. Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2011;10(10):891-7
25. Kinfe TM, Schuss P, Vatter H. Occipital nerve block prior to occipital nerve stimulation for refractory chronic migraine and chronic cluster headache: Myth or prediction? Cephalalgia 2014. [Epub ahead of print
26. Lipton R, Goadsby P, Cady R, et al. PRISM study: occipital nerve stimulation for treatment-refractory migraine. Cephalalgia 2009;29(suppl 1):30
27. Saper JR, Dodick DW, Silberstein SD, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia 2011;31(3):271-85

• **The first published RCT showing promising results of invasive occipital nerve stimulation for refractory chronic migraine management.**

28. Silberstein S, Dodick D, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter,

double-blinded, controlled study. Cephalalgia 2012;32(16):1165-79

•• **This other RCT involves a high number of chronic migraine patients treated with invasive occipital nerve stimulation (iONS). Even if the primary endpoint was not achieved, the 30% responder rate was significant in the iONS arm. Thus, this points out that iONS has a place in refractory chronic migraine treatment after failure of non invasive therapies.**

29. Dodick D, Silberstein S, Huh B, et al. Evidence for long-term efficacy of peripheral nerve stimulation of occipital nerves in the management of chronic migraine. Cephalalgia 2013;33(Suppl 8):58

• **This is the first long-term follow-up study of chronic migraine patients treated with iONS, involving the population of the abovementioned study (reference 28), and suggesting a sustained efficacy of iONS in these patients.**

30. Paemeleire K, Van Buyten JP, Van Buynder M, et al. Phenotype of patients responsive to occipital nerve stimulation for refractory head pain. Cephalalgia 2010;30(6):662-73

• **This trial highlights the important issue of acute medication overuse in chronic headache patients treated with iONS, as the rate of iONS responders was lower in the drug abusers' subpopulation.**

31. Matharu MS, Bartsch T, Ward N, et al. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 2004; 127(Pt 1):220-30

32. Magis D, Bruno MA, Fumal A, et al. Central modulation in cluster headache patients treated with occipital nerve stimulation: an FDG-PET study. BMC Neurol 2011;11(1):25

33. Reed KL, Black SB, Banta CJ 2nd, Will KR. Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. Cephalalgia 2010;30(3): 260-71

34. Reed KL, Will KR, Chapman J, Richter E. Combined occipital and supraorbital neurostimulation for chronic migraine headaches: an extended case series. Cephalalgia 2011;31(suppl 1):98

35. Khan S, Schoenen J, Ashina M. Sphenopalatine ganglion neuromodulation in migraine: what is the rationale? Cephalalgia 2014;34(5):382-91

36. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia 2013; 33(10):816-30

• **This RCT demonstrates the efficacy of sphenopalatine ganglion stimulation in cluster headache, another primary headache. For several (patho) physiological reasons, invasive sphenopalatine ganglion stimulation could be effective in a subpopulation of chronic migraine patients and a study is thus worthwhile.**

37. Schoenen J, Di Clemente L, Vandenheede M, et al. Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 2005;128(Pt 4):940-7

38. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48(5): 1398-403

39. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994; 117(Pt 4):847-58

40. Bohotin V, Fumal A, Vandenheede M, et al. Effects of repetitive transcranial magnetic stimulation on visual evoked potentials in migraine. Brain 2002; 125(Pt 4):912-22

•• **This trial demonstrates that repetitive transcranial magnetic stimulation (rTMS) of the visual cortex is able to normalize the electrophysiological abnormalities usually found in migraineurs in that brain area.**

41. Fumal A, Coppola G, Bohotin V, et al. Induction of long-lasting changes of visual cortex excitability by five daily sessions of repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers and migraine patients. Cephalalgia 2006;26(2):143-9

• **This study shows that repeated sessions of rTMS can durably modify the activity of the visual cortex, suggesting the interest of rTMS use in migraine therapy.**

42. Brighina F, Piazza A, Vitello G, et al. rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J Neurol Sci 2004;227(1):67-71

43. Conforto AB, Amaro E Jr, Goncalves AL, et al. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. Cephalalgia 2014;34(6):464-72

44. Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. J Neurol 2013; 260(11):2793-801

45. Teepker M, Hotzel J, Timmesfeld N, et al. Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. Cephalalgia 2010;30(2):137-44

46. Magis D, Vigano A, Sava S, et al. Pearls and pitfalls: electrophysiology for primary headaches. Cephalalgia 2013;33(8):526-39

47. Schoenen J. Is chronic migraine a never-ending migraine attack? Pain 2011; 152(2):239-40

48. Sasso d'Elia T, Vigano A, Fataki M, et al. Quadripulse repetitive transcranial magnetic stimulation of visual cortex for chronic migraine prevention: a pilot trial. Cephalalgia 2013;33(8 Suppl):49

• **Using a special rTMS paradigm supposed to induce a longer lasting brain modulation, this trial suggests the efficacy of visual cortex neuromodulation in migraine, especially its usefulness as add-on therapy in chronic migraine. It also shows that rTMS efficacy persists at least 1 month after the treatment. A RCT is thus warranted.**

49. Hamada M, Terao Y, Hanajima R, et al. Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. J Physiol 2008;586(16): 3927-47

50. Keeser D, Padberg F, Reisinger E, et al. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. Neuroimage 2011;55(2):644-57

51. Polania R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp 2011. [Epub ahead of print]

52. Coppola G, Ambrosini A, Di Clemente L, et al. Interictal abnormalities of gamma band activity in visual evoked responses in migraine: an indication of thalamocortical dysrhythmia? Cephalalgia 2007;27(12): 1360-7

53. Dasilva AF, Mendonca ME, Zaghi S, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache 2012;52(8):1283-95

54. Antal A, Kriener N, Lang N, et al. Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine. Cephalalgia 2011;31(7):820-8

55. Vigano A, D'Elia TS, Sava SL, et al. Transcranial Direct Current Stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine. J Headache Pain 2013;14(1):23

• **This open trial, based on an electrophysiological rationale, shows the efficacy of transcranial direct current stimulation in episodic migraine prevention.**

56. Tepper SJ, Rezai A, Narouze S, et al. Acute treatment of intractable migraine with sphenopalatine ganglion electrical stimulation. Headache 2009;49(7):983-9

57. Lipton RB, Dodick DW, Silberstein SD, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 2010;9(4):373-80

•• **This RCT demonstrates the efficacy of visual cortex single pulse TMS in migraine with aura acute treatment, using a portable user-friendly TMS device.**

58. Odobescu S, Rotaru L, Moldovanu I, et al. Non-pharmacologic acute treatment of chronic migraine patients by transcranial cerebral electrical stimulation vs placebo. Cephalalgia 2011;31(suppl 1):101

59. Magis D, Gerardy PY, Remacle JM, Schoenen J. Sustained effectiveness of occipital nerve stimulation in drug-resistant chronic cluster headache. Headache 2011; 51(8):1191-201

60. Thorlund K, Mills EJ, Wu P, et al. Comparative efficacy of triptans for the abortive treatment of migraine: a multiple treatment comparison meta-analysis. Cephalalgia 2014;34(4):258-67

61. Gratton C, Lee TG, Nomura EM, D'Esposito M. Perfusion MRI indexes variability in the functional brain effects of theta-burst transcranial magnetic stimulation. PLoS One 2014;9(7):e101430

62. Song JH, Youn DH. Theta-burst stimulation induces LTP at excitatory and inhibitory synapses in the spinal trigeminal subnucleus interpolaris. Neurosci Lett 2014;574:1-5