Review

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
0(0) 1–11

DOI: 10.1177/0333102416636022
cep.sagepub.com

SAGE

Noninvasive neurostimulation methods for migraine therapy: The available evidence

Jean Schoenen[1], Baschi Roberta[2], Delphine Magis[1] and Gianluca Coppola[3]

Abstract

Background: Migraine is one of the most disabling neurological disorders. The current pharmacological armamentarium is not satisfying for a large proportion of patients because the responder rate does not exceed 50% on average and the most effective drugs often induce intolerable side effects. During recent years, noninvasive central and peripheral neuromodulation methods have been explored for migraine treatment.

Overview: A review of the available evidence suggests that noninvasive neuromodulation techniques could be beneficial for migraine patients. The transcranial stimulation methods allow modulating selectively cortical activity and can thus be curtailed to the patient's pathophysiological profile, while transcutaneous stimulation of pericranial nerves likely modulates central pain control centers. Occipital single-pulse transcranial magnetic stimulation and transcutaneous supraorbital stimulation have the strongest evidence respectively for acute and preventive treatment. Transcranial direct current stimulation and repetitive magnetic stimulation are promising in pilot studies, but large sham-controlled trials are not yet available.

Conclusions: The noninvasive neurostimulation methods are promising for migraine treatment and devoid of serious adverse effects allowing their combination with drug therapies. Their application in clinical practice will depend on the industry's capacity to develop portable and user-friendly devices, and on the scientists' capacity to prove their efficacy in randomized sham-controlled trials.

Keywords

Transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, transcutaneous supraorbital stimulation

Date received: 27 October 2015; revised: 12 January 2016; accepted: 6 February 2016

Background

Noninvasive neurostimulation methods used in migraine target either transcutaneously peripheral nerves or transcranially the brain itself. The rationale for the two is different (see Coppola et al. (1) in this issue). Peripheral nerve stimulation has been used for a long time in chronic pain disorders and, like percutaneous occipital nerve stimulation in refractory chronic cluster headache, it probably acts by modulating central pain control areas (2).

The rationale for using transcranial neurostimulation methods in migraine therapy is based on the fact these methods are susceptible to normalizing the abnormalities of cortical responsivity found in migraine patients between attacks (see Coppola et al. (1) in this issue).

The noninvasive neurostimulation methods are of particular interest in migraine because they are much better tolerated and accepted than invasive techniques and hence must not be restricted like the latter to the

[1]Liège University, Headache Research Unit, University Department of Neurology, Belgium
[2]Headache Center and Unit of Neurology and Neurophysiopathology, University of Palermo, Italy
[3]G.B. Bietti Foundation IRCCS, Department of Neurophysiology of Vision and Neurophthalmology, Italy

Corresponding author:
Jean Schoenen, University Department of Neurology, CHR Citadelle, Bld. du 12ème de Ligne 1, B – 4000 Liège, Belgium.
Email: jschoenen@ulg.ac.be

most disabled refractory patients. At present, however, few randomized sham-controlled trials are available and the data presented for several neurostimulation methods or devices must therefore be considered with some reservation. In this review we have summarized the advances in the use of noninvasive neurostimulation methods for the acute and prophylactic therapy of migraine.

Transcranial magnetic stimulation (TMS)

Single-pulse TMS (sTMS) (Table 1). In an open-label study, Clarke et al. (3) evaluated the efficacy and tolerability of one to three treatments of two pulses of TMS at low or high intensity applied over the perceived pain area for the acute treatment of migraine attacks without aura (MO) or over the visual cortex for attacks with aura (MA). Pain intensity, the primary outcome measure, was reduced by 75% up to 20 minutes post-TMS. Moreover, 32% of patients reported no further headache for up to 24 hours after one treatment, 29% after two treatments and 40% after three treatment sessions (3).

In a multicenter, randomized, double-blind, parallel-group, sham-controlled study, Lipton et al. (4) assessed the efficacy of a novel portable TMS device (Neuralieve®, eNeura, USA) applied over the visual cortex in 164 MA patients ($n = 82$ sham), treating up to three attacks with aura over three months within one hour of aura onset. Real sTMS was superior to sham for pain freedom at two hours (39% vs. 22% respectively, i.e. 17% of therapeutic gain), and for sustained pain freedom at 24 hours (29% vs. 16%) and 48 hours (27% vs. 13%). There was no statistical difference between the real sTMS and sham stimulation groups for the combination of no or mild pain at two hours, use of rescue medication, consistency of effect, patients' global assessment of pain or the Migraine Disability Assessment Score Questionnaire (MIDAS) score (4). Because of the rather small effect size compared to placebo and the lack of significant changes in patients' satisfaction and disability, one may question the clinical usefulness of sTMS in MA. In a post-market pilot program in the United Kingdom based on telephone interviews, Bhola et al. (5) evaluated sTMS in 190 episodic (EM) or chronic migraine (CM) patients who had previously found acute medications intolerable, ineffective, or contraindicated. Sixty-two percent of patients reported the device was effective in reducing or alleviating their migraine headache, and 59% reported a reduction in the number of headache days after 12 weeks of treatment. No serious adverse events occurred, but the discontinuation rate was higher than expected (55%) probably because of dissatisfaction. Besides the facts that this survey is non-controlled, based on telephone interviews for follow-up and not based on headache diaries, other major weaknesses are inclusion of patients taking preventive antimigraine drugs or overusing acute medications. At this stage, sTMS can thus not be considered to have an established utility for migraine treatment in clinical practice.

Repetitive TMS (Table 2). Repetitive TMS (rTMS) has been tested as a preventive treatment both for EM and for CM with equivocal results. In an open-label, sham-controlled study in which 12 high-frequency (HF) (20 Hz) daily rTMS sessions were applied over the left dorsolateral prefrontal cortex (DLPFC), Brighina et al. (6) demonstrated the potential safety and efficacy of rTMS as headache prophylaxis in 12 CM patients (six real, six sham). They found a significant reduction of attack frequency at two months with rTMS (−53%) compared to sham (−7%, therapeutic gain of 46%) and a parallel reduction of acute medication intake and headache severity, without side effects.

In a recently published study, a group of 14 CM patients (seven real, seven sham) underwent a total of 23 sessions of either HF (10 Hz) rTMS or sham treatment over the left DLPFC within eight weeks. Real rTMS was less effective in reducing headache days than sham (−15% vs. −58.1%), with a negative therapeutic gain (−43.1%), while pain intensity, depression and anxiety indexes, as well as MIDAS scores, decreased equally in both groups (10). Inclusion of patients, most of whom were acute medication overusers and taking prophylactic drugs, is a major weakness of this study. This may account for negative outcome, although the authors argue that activation of the DLPFC might have attenuated the placebo effect.

In a group of EM patients ($N = 27$), Teepker et al. (7) failed to find a significant reduction of headache days after five sessions of low-frequency rTMS versus sham over the vertex over eight weeks. However, severity of headache, functional disability and number of acute rescue medications were significantly lower in the real rTMS group compared to the sham group.

Another group of researchers administered a total of three sessions of HF rTMS or sham over the left frontal cortex on alternate days first in an open-label study (8) and thereafter in a randomized, placebo-controlled, double-blind trial (9). In the latter trial, they enrolled a heterogeneous group of 100 patients with various diagnoses: 93 MO, 7 MA, among whom 60 were CM and 28 medication-overuse headache (MOH) (sham $n = 50$ or rTMS $n = 50$). They observed after one month a significant improvement in headache frequency in the rTMS group (−78.7%) compared to sham (−33.3%) and in headache intensity (−76.6% vs. −27.1%). The clinical improvement was especially pronounced in CM patients. Functional disability and

Table 1. Single-pulse TMS studies as acute treatment.

Authors	Study	Treatment	Device	Stimulated area	Outcome measures	Participants	Results	Side effects
Clarke et al. (3)	Open-label	One to three trials of two pulses TMS at low or high intensity	Caldwell #MES-10, round coil	MO: over perceived pain area MA: V1	(a) Pain intensity (five-point Likert-type scale); (b) headache occurrence up to 24 hours post-TMS	MA ($n=10$), MO ($n=25$), probable migraine ($n=6$)	(a) ↓ Post-stimulation pain intensity of 75% up to 20 minutes post-TMS; (b) 32% of those patients receiving one trial reported no further headache; 29% with two trials, 40% with three trials	Dizziness ($n=1$) Drowsiness ($n=1$) Feeling tired ($n=2$)
Lipton et al. (4)	Multicenter randomized, double-blind, parallel-group, two-phase, sham-controlled	To treat up to three attacks over three months while experiencing aura (within one hour of onset)	Neuralieves TMS device	V1	Primary: (a) Pain-free response two hours after first attack; (b) non-inferiority at two hours for nausea, photophobia, and phonophobia Secondary: (a) % of patients who had mild or no pain at two hours; (b) % with sustained pain free at 24 hours and 48 hours; (c) % who needed rescue drugs; (d) consistency of pain-free episodes in two of three aura episodes; (e) patient's global assessment of pain relief, and proportion with vomiting	MA ($n=164$): sham ($n=82$) or sTMS ($n=82$)	Primary: (a) ↑ Pain free after two hours with sTMS (39%) than sham (22%); 17% therapeutic gain; (b) non-inferiority shown for nausea, photophobia and phonophobia. Secondary: (a) Not different; (b) ↑ pain free at 24 hours with sTMS (29%) compared with sham (16%); at 48 hours with sTMS (27%) compared with sham (13%); (c) not different; (d) not different; (e) not different.	Headache (sham $n=1$/sTMS $n=2$) Migraine (0/2) Sinusitis (1/2) Paresthesia (2/0)
Bhola et al. (5)	Open-label, telephone survey	One or two pulses as early as possible. They could treat on as many acute migraine days as they wished over 12 weeks.	Spring TMS device	V1	N/A	M = 190: MO or MA = 59, CM = 131 (87 with MOH)	62% of patients reported device effective at reducing or alleviating migraine pain, 59% at reducing number of headache days, and 72% reported lower HIT-6 score post-TMS after 12 weeks' use.	Transient light-headedness ($n=38$) Tinnitus, dizziness or tingling over back of head ($n=19$) Worsening of migraine symptoms ($n=13$) Neck and upper shoulder pain ($n=1$)

CM: chronic migraine; MA: migraine with aura patients; MO: migraine without aura patients; MOH: medication-overuse headache; N/A: not applicable; sTMS: single-pulse TMS; TMS: transcranial magnetic stimulation; HIT-6: Headache Impact Test; M: migraine patients.

Table 2. Repetitive TMS studies as preventive treatment.

Reference	Study	Treatment	Device	Stimulated area	Outcome measures	Participants	Results	Side effects
Brighina et al. (6)	Open-label, sham-controlled	12 High-frequency (20 Hz) rTMS daily sessions, each consisting of 10 trains of 2 seconds' duration, separated by 30 seconds' pause, given at 90% MT	Cadwell HF-magnetic stimulator (figure-of-eight coil)	Left dorsolateral prefrontal cortex	(a) Primary: frequency of attacks and the number of abortive pills per month; (b) secondary: headache index (frequency * intensity)	CM ($n=12$): sham ($n=6$) or rTMS ($n=6$)	(a) ↓ attack frequency at two months with rTMS (53%) than sham (7%); 46% therapeutic gain; (b) ↓ abortive pills and headache index with rTMS, not with sham	No side effects
Teepker et al. (7)	Placebo-controlled, blinded study	Total of five sessions of either LF-(1 Hz) rTMS (two trains of 500 pulses, separated by 1 minute's pause, given at resting MT) or sham within eight weeks	MagPro compact, Dantec (round coil)	Over vertex (Cz)	(a) Primary: attack frequency; (b) secondary: migraine days, migraine hours, pain intensity and analgesic intake	M ($N=27$; 13 MA and 14 MO): sham ($n=13$) or rTMS ($n=14$)	(a) Moderate significant reduction in headache days after rTMS, but not different compared to sham; (b) all secondary outcome variables did not differ significantly between rTMS and sham stimulation	No side effects
Misra et al. (8)	Open-label study	Total of three sessions of HF-(10 Hz) rTMS (10 trains of 60 pulses, separated by 45 seconds, given at 70% MT) or sham on alternate days	Magstim Rapid-2 (Whiteland, Walsh, UK) with an air-cooled figure-of-eight coil of 7 cm diameter.	Left frontal cortex	(a) Primary: headache frequency; (b) secondary: severity of headache, functional disability, rescue medication, migraine index	M medically refractory ($n=51$)	(a) ↓ Headache frequency at one month with rTMS (80.4%); (b) all secondary outcome measures were significantly lower in rTMS group compared to sham group	No side effects
Misra et al. (9)	Randomized, placebo-controlled double-blind study	Total of three sessions of HF-(10 Hz) rTMS (10 trains of 60 pulses, separated by 45 seconds, given at 70% MT) or sham on alternate days	Magstim Rapid-2 (Whiteland, Walsh, UK) with an air-cooled figure-of-eight coil of 7 cm diameter	Left frontal cortex	(a) Primary: headache frequency, pain frequency*severity;(b) secondary: severity of headache, functional disability, rescue medication	M ($n=100$, 93 MO, 7 MA, 60 CDH, 28 MOH): sham ($n=50$) or rTMS ($n=50$)	(a) ↓ Headache frequency at one month with sham (33.3%) than rTMS (78.7%); –45.4% therapeutic gain; improvement in headache severity * frequency in rTMS group (CDH > episodic M) compared to	Drowsiness ($n=1$) General discomfort with rTMS (all)

(continued)

Table 2. Continued.

Reference	Study	Treatment	Device	Stimulated area	Outcome measures	Participants	Results	Side effects
							sham; (b) all secondary outcome measures significantly lower in rTMS group compared to sham group	
Conforto et al. (10)	Randomized, double-blind, parallel-group, single-center, clinical trial	Total of 23 sessions of either HF-(10 Hz) rTMS (32 trains of 5 seconds' duration, separated by 30-second pause, given at 110% MT) or sham within eight weeks	MagPro X100 (Alpine Biomed) (figure-of-eight coil)	Left dorsolateral prefrontal cortex	(a) Primary: number of headache days; (b) secondary: pain intensity, MIDAS, BDI, STAI	CM ($n = 14$): sham ($n = 7$) or rTMS ($n = 7$)	(a) ↓ Headache days at two months with sham (58.1%) than rTMS (15.0%); – 43.1% therapeutic gain; (b) ↓ pain intensity at two months in both treatment groups; ↓ BDI at two months with sham, but not with rTMS; ↓ STAI and MIDAS in both groups	Worsening, onset of headache, or pain under coil Sleepiness

BDI: Beck Depression Inventory; CDH: chronic daily headache; CM: chronic migraine; HF: high frequency; LF: low frequency; M: migraineur patient; MA: migraine with aura patient; MIDAS: Migraine Disability Assessment Score Questionnaire; MO: migraine without aura patient; MT: motor threshold; rTMS: repetitive transcranial magnetic stimulation; STAI: state-trait anxiety inventory; DCS: transcranial direct current stimulation.

use of acute rescue medication were significantly lower in the rTMS group. Again, a major shortcoming of this study was that it included patients with medication overuse and taking preventive antimigraine drugs.

Finally, in a proof-of concept study based on the neurophysiological evidence that the sensory cortices are hyperexcitable in CM, inhibitory quadripulse rTMS was applied over the visual cortex twice per week for one month in 12 CM patients. The treatment significantly decreased headache and migraine days, total headache duration, headache intensity and acute medication use. Six out of 12 patients (40%) had a $\geq$50% reduction in migraine days and nine patients (60%) reversed from CM to EM (11).

To summarize, rTMS could thus be effective in migraine prophylaxis but it is difficult to implement in clinical practice because of the non-portability of the devices and their high cost.

Transcranial direct current stimulation (tDCS) (Table 3). tDCS has over rTMS the advantage that it can be applied with devices that are inexpensive and portable.

In two studies, repeated cathodal tDCS, i.e. an inhibitory current, was applied over the visual cortex without significant change in migraine attack frequency. The first was a randomized, sham-controlled trial in 26 migraine patients (12 MO, 14 MA) who underwent three daily 15-minute sessions/week of active ($n = 15$) (cathode at Oz, anode at Cz) or sham tDCS ($n = 15$) for three weeks. Neither tDCS nor sham stimulation significantly reduced migraine attacks or duration at two months (12). In the second randomized, double-blind, parallel-group controlled pilot trial, Rocha et al. (16) administered 12 20-minute sessions (three times a week for four weeks) of cathodal or sham tDCS over the visual cortex in 15 migraine patients (10 real, 5 sham) and likewise found no difference between sham and verum in change of attack frequency, duration or intensity.

By contrast, in a proof-of-concept study based on the rationale that between attacks the visual cortex of migraine patients has a reduced pre-activation level, but an increased responsivity with repeated stimulation (see Coppola et al. (1) this issue), anodal tDCS, thus an activating stimulation, over the occiput was beneficial in EM patients (15). In 10 MO patients who underwent 10 15-minute sessions (twice a week) of anodal tDCS over the visual cortex for eight weeks, there was a significant reduction in attack frequency (−38%), migraine days (−48%), attack duration (−60%) and acute drug intake (−28%) at month 2 of follow-up, i.e. one month post-treatment. Besides being open and uncontrolled, this study suffers from the inclusion of some patients taking preventive medications and the results need to be confirmed in a randomized sham-controlled trial (15).

Two small studies using anodal tDCS over the primary motor cortex M1 reported a positive outcome. In 13 CM patients treated with 10 20-minute sessions of anodal ($N = 8$) or sham ($N = 5$) tDCS over M1 for four weeks, a significant reduction of headache intensity was found after four months in the real tDCS group and a trend for reduced migraine attack duration (13). Auvichayapat et al. treated 37 EM patients with anodal ($N = 20$) or sham ($N = 17$) tDCS for 20 minutes over 20 consecutive days. They observed significant reductions favoring tDCS over sham at 4, 8, and 12 weeks for attack frequency, headache intensity and number of abortive medications taken (14).

To sum up, tDCS can thus be considered a more interesting therapeutic option than rTMS because it is portable, more user-friendly and affordable.

Transcutaneous peripheral (cranial) nerve stimulation

Neurostimulation of pericranial nerves with subcutaneous implanted electrodes has been explored as therapy for primary headaches since more than 30 years (see Ambrosini et al. this issue). Percutaneous suboccipital nerve stimulation (ONS) was found useful for CM in several non-controlled studies and case reports, but the global effect in three sham-controlled studies was far from being convincing (17–19), and adverse effects were rather frequent. These methods should thus be restricted to the most-disabled CM patients. Technological advances during the last decade have led to the development of noninvasive, transcutaneous stimulators of peripheral nerves that can be used also in less-disabled patients and are deemed to have comparable efficacy to the minimally invasive methods.

Trigeminal (and suboccipital) stimulation with the Cefaly® device

A novel transcutaneous supraorbital electrostimulation device, the Cefaly® (Cefaly Technology, Liège, Belgium), has recently been approved for the preventive treatment of migraine by the United States Food and Drug Administration. This decision was chiefly based on the results of an investigator-initiated, randomized, double-blind, sham-controlled trial (PREMICE) coordinated by the Belgian Headache Society (20). The study included 67 migraine patients with at least two migraine attacks per month. After a one-month baseline period, patients were randomized to a verum or a sham stimulator for three months and asked to apply one 20-minute stimulation session per day. At the end of this treatment period, there was a greater reduction in the average monthly number of migraine days in the verum group (from 6.9 to 4.8) than in the sham group

Table 3. tDCS studies as preventive treatment.

Authors	Study	Treatment	Device	Stimulated area	Outcome measures	Participants	Results	Side effects
Antal et al. (12)	Randomized sham-controlled trial	All patients received sham stimulation during initial three weeks. Three daily sessions/week of active (cathodal) or sham tDCS for 15 minutes with 1 mA over successive three weeks	NeuroConn, Ilmenau, Germany	Cathode over V1 (Oz) and anode over Cz	(a) Migraine attacks; (b) migraine-related days, mean duration of attacks, intensity of pain	M ($n=26$, 12 MO, 14 MA): sham ($n=15$) or tDCS ($n=15$)	(a) Both tDCS and sham did not significantly reduce migraine attacks at two months; no significance differences observed between tDCS and sham; (b) ↓ migraine-related days, attack duration and pain intensity with tDCS than sham, but (with exception of pain intensity) between-groups comparison not different	Mild tingling sensation (78.1% tDCS, 71.0% sham) Moderate itching (21.3% tDCS, 28.4% sham) Fatigue (14.3 tDCS, 28.4% sham) Tiredness (7.1% tDCS, 42.6 sham) Headache (21.3% tDCS, 35.5% sham)
Dasilva et al. (13)	Randomized sham-controlled trial	Ten sessions of active (anodal) or sham tDCS for 20 minutes with 2 mA over four weeks	Magstim	Anode over M1 and cathode over contralateral supra-orbital area	(a) Perception of daily pain measured by VAS; (b) length of migraine episodes, Patient Global Assessment (PGA), and Clinical Global Impression (CGI)	CM ($n=13$): sham ($n=5$) or tDCS ($n=8$)	(a) ↓ Pain intensity after four months with tDCS than sham; (b) trend for ↓ length of migraine episodes and improvement of PGA with tDCS; no differences for CGI.	No side effects
Auvichayapat et al. (14)	Randomized sham-controlled trial	Active (anodal) or sham tDCS for 20 minutes with 1 mA over 20 consecutive days		Anode over M1	(a) Attack frequency; (b) pain intensity, abortive medications	M ($n=37$): sham ($n=17$) or tDCS ($n=20$)	(a) ↓ Attack frequency at 4, 8, and 12 weeks with tDCS than sham; (b) ↓ pain intensity (at 4, 8, and 12 weeks) and no abortive medications (at four and eight weeks) than sham	No side effects
Viganò et al. (15)	Open-label study	Ten sessions (twice a week) of active (anodal) tDCS for	NeuroConn, Ilmeanu, Germany	Anode over V1 (Oz) and	(a) Attack frequency, migraine days, pain intensity, attack	MO ($n=10$)	(a) ↓ Attacks frequency (38%), migraine days	- Light itching sensation

(continued)

Table 3. Continued.

Authors	Study	Treatment	Device	Stimulated area	Outcome measures	Participants	Results	Side effects
		15 minutes with 1 mA over eight weeks		cathode over the chin	duration, acute drug intake		(48%), attack duration (60%), and acute treatment intake (28%) at two months	
Rocha et al. (16)	Randomized, double blinded, parallel-group controlled pilot trial	Twelve sessions (three times a week) of active (cathodal) or sham tDCS for 20 minutes with 2 mA over four weeks	NeuroConn, Germany	Cathode over VI (Oz), anode over vertex (Cz)	(a) Attack frequency, pain intensity, attack duration, acute drugs intake; (b) phosphine threshold (PT)	M ($n = 15$): sham ($n = 5$) or tDCS ($n = 10$)	(a) No difference found in attack frequency, pain intensity and duration between tDCS and sham stimulation. ↓ Acute drugs intake with tDCS than sham; (b) No difference in PT	No side effects

CM: chronic migraine; M: migraine patients; MA: migraine with aura; MO: migraine without aura; N.S.: not specified; PT: phosphine threshold; tDCS: transcranial direct current stimulation; VAS: visual analog scale.

(from 6.5 to 6.2) and a higher percentage of 50% responders (38.2% vs 12.1%) with a therapeutic gain of 26.1%. This was accompanied by a reduction in the mean number of triptans taken per month in the verum group. The effect size was considered to be comparable to that of several preventive antimigraine drugs (20). It was inferior to that reported in the pooled placebo-controlled topiramate trials, but was not accompanied by any cumbersome side effects nor any drop-outs, while in the topiramate trials 50% of patients had side effects that led to a drop-out rate of one out of four. Additional statistical analyses (21) showed that age and disease duration did not affect outcome, but that the effect size was directly related to the number of migraine days during baseline. This suggests that Cefaly® might be more beneficial for patients with more frequent migraines. Trials on its effect in chronic migraine patients are underway (ClinicalTrials.gov identifier: NCT02342743).

In a post-marketing survey of 2313 triptan participants who rented the Cefaly® over the Internet for six weeks after which they had to buy it or send it back, 53.4% found it effective and purchased it (22). Surprisingly, out of the 46.6% dissatisfied participants who sent it back, only 40% used it for the recommended time, which suggests that the true (''per protocol'') non-responder rate could be as low as 18.6%. In the survey only 4.3% of patients reported at least one adverse event during treatment with the Cefaly®, none of them serious and all reversible. The most frequent was intolerance to the paresthesias induced by the electrical stimulation, which led in some cases to interruption of treatment. Other adverse events included drowsiness during treatment and reversible skin irritation under the forehead electrode. The efficacy (50% responder rate of 75%) and excellent tolerability of Cefaly® was recently confirmed in a small, open-label, 60-day trial on 24 MO patients (23).

In pilot trials with the Cefaly® both its effect on attack prevention and acute attack treatment was examined (24). In 10 patients a total of 30 attacks were treated with a stimulation protocol that differed from that used for prevention mainly by a higher stimulation frequency (100 Hz). Within 30 minutes the Cefaly® provided total migraine relief without rescue medication in 13% of attacks and partial relief with rescue medication in 45%. Randomized trials of the efficacy of Cefaly® as an acute migraine treatment are in progress (ClinicalTrials.gov identifier NCT02411513).

The Cefaly® device can also be used to deliver transcutaneous suboccipital neurostimulation (tONS). Preliminary pilot studies suggest that tONS with the Cefaly® might be effective in CM patients (ClinicalTrials.gov identifier NCT02307071) (25).

To summarize, supraorbital neurostimulation with the Cefaly® is effective as preventive treatment in EM and has excellent tolerability and a favorable safety profile (see Riederer et al. for a review (26)). It might also be useful for acute attack treatment and for chronic migraine, but these effects remain to be confirmed in sham-controlled trials. As with other transcutaneous neurostimulation devices, adherence to treatment may be problematic in the long term.

Vagus nerve stimulation (VNS) with the gammaCore®

As mentioned by Coppola et al. (this issue (1)), circumstantial evidence that VNS could be useful in migraine treatment comes from reports of several patients who were treated with an implanted VNS system for refractory epilepsy and had comorbid migraine that improved over time. Further development of VNS in migraine therapy was halted by the invasiveness of the procedure and by resources prioritizing by the manufacturer. VNS gained renewed interest when noninvasive devices were invented allowing transcutaneous stimulation of the vagus nerve (tVNS) in the neck or of its auricular branches in the outer ear. The device with the most encouraging results at present is the gammaCore® (Electrocore, USA) and is applied in the neck. In an open, proof-of-concept study (27), 30 migraine patients (10 with and 20 without aura) treated up to four moderate/severe or mild attacks with the gammaCore® applied over the right cervical branch of the vagus nerve for two 90-second sessions separated by 15 minutes. The therapeutic response was moderate, since 22% of patients who treated moderate/severe attacks and 38% with mild attacks were pain free after two hours, while 43% of patients who treated moderate/severe attacks had pain relief after two hours. In another open-label study, Barbanti et al. (28) studied tVNS over the neck with the gammaCore® for the treatment of migraine attacks in patients with high-frequency episodic migraine ($N = 14$, HFEM) or CM ($N = 36$, CM). After two 90-second gammaCore® sessions separated by 3 minutes, 56.3% of patients reported pain relief at one hour (35.4% were pain free) and 64.6% at two hours (39.6% were pain free). They observed a trend toward greater efficacy in patients with HFEM than in patients with CM. After two hours, pain relief was obtained by 62.5% of patients (78.6% in HFEM, 55.9% in CM) and a pain-free state by 33.3% (50% in HFEM, 26.5% in CM) (see Table 4). However, this study has several major shortcomings, such as the large variability of number of treated attacks between patients (from one to six), and the inclusion of patients with medication overuse and preventive migraine treatment. In a recent monocentric, randomized, controlled, double-blind study, a group of CM patients were randomized to receive 25 Hz or 1 Hz stimulation of the sensory vagal afferents in the outer ear with a battery-driven stimulator (NEMOS® Cerbomed, Germany) for 4 hours/day during three months (29). Surprisingly, the authors found a significantly larger decrease in monthly headache days at three months in the 1 Hz group (−36.4%) than in the 25 Hz group (−17.4%); there was no reduction in headache intensity, nor in medication intake or disability scores. The number of responders was 29.4% in the 1 Hz group and 13.6% in the 25 Hz group. There is no explanation for these unexpected results and further studies are clearly necessary.

Overall, large sham-controlled trials are needed in order to validate transcutaneous VNS as an effective acute and/or preventive treatment of migraine.

Table 4. Summary of recommendations and levels.

Method	Level of recommendation (30)	Grade (31)
sTMS	I A	High
rTMS	II B	Moderate
tDCS	II B	Moderate
Cefaly®	I A	High
VNS	IV C	Low

rTMS: repetitive transcranial magnetic stimulation; sTMS: single-pulse transcranial magnetic stimulation; tDCS: transcranial direct-current stimulation; VNS: vagus nerve stimulation.

Conclusion

Noninvasive neurostimulation methods are promising for the treatment of EM and CM because of the available data on clinical efficacy and their excellent tolerability and safety. For some of them the efficacy-side effect profile may thus be better than for certain pharmacological treatments. There is strong evidence that transcutaneous pericranial nerve stimulation with the Cefaly® is effective in the prevention of EM; the favorable safety profile remains to be confirmed in long-term studies; the results of controlled trials in CM and in acute treatment are eagerly awaited. tVNS with the gammaCore® lacks at present evidence for efficacy in acute or preventive treatment of migraine. Beneficial effects of attack treatment were found in open-label trials.

By contrast, the transcranial magnetic (TMS) and direct current (tDCS) neurostimulation techniques allow us to target specific cortical areas and to influence them in opposite directions. The rationale for their use in migraine is thus of the uttermost importance and conditions treatment outcome. The stimulation protocol and

site are crucial, as cortical changes vary not only over the migraine cycle, but also with attack frequency and reversal from EM to CM (32,33). There is at present evidence for an effect on migraine headache of single-pulse TMS over the occipital cortex in MA and possibly in MO, but the overall effect size seems small. Repetitive TMS over the dorsolateral prefrontal cortex, the motor cortex or the visual areas might be effective in EM and CM depending on the stimulation protocol, but large sham-controlled trials are lacking. Although it can induce long-lasting changes of the underlying cortex, rTMS is difficult to implement in clinical practice because of the cost and non-portability of the devices. tDCS does not have these handicaps, since the devices are not expensive and portable. Controlled studies based on the rationale that in migraine the cerebral cortex is hyperexcitable and hence using cathodal tDCS inhibition of the visual areas found no significant therapeutic effect. This contrasts with positive proof-of-concept studies reasoning that the cortex is not hyperexcitable, but hyper-responsive in EM between attacks, and that the visual areas should thus be activated with anodal tDCS. A sham-controlled trial, however, confirming this beneficial effect in EM prevention is not yet available. Finally, anodal tDCS over the primary motor cortex was found effective for the preventive treatment of EM and CM in small, placebo-controlled trials.

There is little doubt that in the near future evidence-based data will be accruing for noninvasive neurostimulation in the various migraine types, but also that novel devices and stimulation protocols will improve their efficacy.

Article highlights

- Noninvasive transcutaneous and transcranial neurostimulation methods seem promising treatments for migraine based on available efficacy data but more randomized sham-controlled trials are needed.
- Thanks to their excellent tolerability and safety, noninvasive neurostimulation methods can be combined with drug treatments and the potential benefit of combining them between each other merits to be explored.
- Transcranial magnetic and direct-current stimulation can selectively influence brain areas while transcutaneous supraorbital or suboccipital stimulation seems to modulate pain control centers. They allow us therefore to target specific facets of migraine pathophysiology.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: JS and DM are supported by funding from the European Union's Seventh Framework programme (2007–2013) under grant agreement no. 602633. GC is supported financially by the Italian Ministry of Health and Fondazione Roma.

References

1. Coppola G, Di Lorenzo C, Serrao M, et al. Pathophysiological targets for non-pharmacological treatment of migraine. *Cephalalgia*, Epub ahead of print 3 December 2015.
2. Magis D, Bruno M, Fumal A, et al. Central modulation in cluster headache patients treated with occipital nerve stimulation: An FDG-PET study. *BMC Neurol* 2011; 11: 25.
3. Clarke B, Upton A, Kamath M, et al. Transcranial magnetic stimulation for migraine: Clinical effects. *J Headache Pain* 2006; 7: 341–346.
4. Lipton R, Dodick D, Silberstein S, 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: 373–380.
5. Bhola R, Kinsella E, Giffin N, et al. Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: Evaluation of outcome data for the UK post market pilot program. *J Headache Pain* 2015; 16: 535.
6. 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: 67–71.
7. Teepker M, Hötzel J, Timmesfeld N, et al. Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. *Cephalalgia* 2010; 30: 137–144.
8. Misra U, Kalita J and Bhoi S. High frequency repetitive transcranial magnetic stimulation (rTMS) is effective in migraine prophylaxis: An open labeled study. *Neurol Res* 2012; 34: 547–551.
9. Misra U, Kalita J and Bhoi S. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: A randomized, placebo-controlled study. *J Neurol* 2013; 260: 2793–2801.
10. Conforto A, Amaro E, Gonçalves A, et al. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. *Cephalalgia* 2014; 34: 464–472.
11. Sasso D'Elia T, Viganò A, Sava S, et al. Theta burst and quadripulse repetitive transcranial magnetic stimulation (rTMS) may have therapeutic potentials in migraine prevention: A proof-of-concept study in healthy volunteers and a pilot-trial in migraine patients. *Front Human Neurosci* 2012; 52.

12. 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: 820–828.
13. Dasilva A, Mendonca M, Zaghi S, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache* 2012; 52: 1283–1295.
14. Auvichayapat P, Janyacharoen T, Rotenberg A, et al. Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial. *J Med Assoc Thai* 2012; 95: 1003–1012.
15. Viganò A, D'Elia T, Sava S, 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: 23.
16. Rocha S, Melo L, Boudoux C, et al. Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: A pilot randomized controlled trial. *J Neurol Sci* 2015; 349: 33–39.
17. Saper J, Dodick D, Silberstein S, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia* 2011; 31: 271–285.
18. 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: 1165–1179.
19. Dodick D, Silberstein S, Reed K, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Long-term results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia* 2015; 35: 344–358.
20. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: A randomized controlled trial. *Neurology* 2013; 80: 697–704.
21. Schoenen J. Addendum to ''Migraine prevention with a supraorbital transcutaneous stimulator: A randomized controlled trial''. *Neurology* 2015; 86: 2–3. WriteClick; Editor's choice.
22. Magis D, Sava S, d'Elia T, et al. Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly® device in headache treatment: A survey of 2,313 headache sufferers in the general population. *J Headache Pain* 2013; 14: 95.
23. Russo A, Tessitore A, Conte F, et al. Transcutaneous supraorbital neurostimulation in ''de novo'' patients with migraine without aura: The first Italian experience. *J Headache Pain* 2015; 16: 69.
24. Gérardy P, Fabry D, Fumal A, et al. A pilot study on supra-orbital surface electrotherapy in migraine. *Cephalalgia* 2009; 29: 134.
25. D'Ostilio K, Nonis R, Sava S, et al. Transcranial direct current stimulation and transcutaneous occipital nerve stimulation in chronic migraine: A pilot-comparison of therapeutic and electrophysiological effects. *American Acad Neurol* 2015; abstract.
26. Riederer F, Penning S and Schoenen J. Transcutaneous supraorbital nerve stimulation (t-SNS) with the Cefaly® device for migraine prevention: A review of the available data. *Pain Ther* 2015; 4: 135–147.
27. 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: 986–993.
28. Barbanti P, Grazzi L, Egeo G, et al. Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: An open-label study. *J Headache Pain* 2015; 16: 542.
29. Straube A, Ellrich J, Eren O, et al. Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): A randomized, monocentric clinical trial. *J Headache Pain* 2015; 16: 543.
30. Brainin M, Barnes M, Baron J, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2004. *Eur J Neurol* 2004; 11: 577–581.
31. Leone M, Brainin M, Boon P, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2012. *Eur J Neurol* 2013; 20: 410–419.32.
32. Coppola G and Schoenen J. Cortical excitability in chronic migraine. *Curr Pain Headache Rep* 2012; 16: 93–100.
33. Magis D, Vigano A, Sava S, et al. Pearls and pitfalls: Electrophysiology for primary headaches. *Cephalalgia* 2013; 33: 526–539.