

# Targeting pericranial nerve branches to treat migraine: Current approaches and perspectives

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## Abstract

**Background:** Migraine is a highly prevalent neurological disorders and a major individual and societal burden. Migraine is not curable at the present time, but it is amenable to acute symptomatic and preventive pharmacotherapies.

**Summary:** Since the latter are frequently unsatisfactory, other treatment strategies have been used or are being explored. In particular, interventions targeting pericranial nerves are now part of the migraine armamentarium. We will critically review some of them, such as invasive and noninvasive neurostimulation, therapeutic blocks and surgical decompressions.

**Conclusions:** Although current knowledge on migraine pathophysiology suggests a central nervous system dysfunction, there is some evidence that interventions targeting peripheral nerves are able to modulate neuronal circuits involved in pain control and that they could be useful in some selected patients. Larger, well-designed and comparative trials are needed to appraise the respective advantages, disadvantages and indications of most interventions discussed here.

## Keywords

Migraine, treatment, surgery, neurostimulation, blocks, pericranial nerves

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## Introduction

Migraine is one of the most common neurological disorders, affecting 18.5% of the general population (1), and it causes marked disability in many patients (2,3). In its episodic form, it is characterized by recurrent attacks of moderate/severe headache associated with nausea and/or vomiting, photophobia and phonophobia (4). In 20–30% of patients the headache is preceded or accompanied at its onset by a sequence of reversible focal neurological symptoms called “aura.” Classically it consists of a scintillating scotoma that can be followed by sensory and language disturbances and, in hemiplegic migraine, by motor symptoms.

Episodic migraine may evolve into chronic migraine when headache days exceed 15 per month with at least eight migraine headache days (4). Chronic migraine is the most disabling form of migraine and affects at least 0.5% of the general population (1).

## Pathophysiology

Migraine is thought to be a central neurovascular disorder. The migraine headache is likely generated in

the trigeminovascular system (TVS) (5) that can be activated by cortical spreading depression (CSD), i.e. slowly propagating waves of brief neuronal and glial depolarization followed by prolonged neuronal inactivation (6,7), which is responsible for the migrainous aura. In migraine without aura the mechanisms underlying TVS activation are still controversial, but a role for dysfunctioning central pain control systems has been suggested (8). The migraine attack is a sequential process, comprising in >30% of patients premonitory symptoms (9,10) accompanied on neuroimaging by activation in the ventral hypothalamus (11).

The predisposition to attack recurrence in migraine is reflected in functional brain changes that fluctuate

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over the migraine cycle, such as those related to the processing of sensory stimuli and cortical reactivity (12), and to mitochondrial energy metabolism (13–15). Migraine is supposed to be a complex polygenic disorder where the genetic load sets a threshold that is influenced by environmental and hormonal factors (16). In chronic migraine there are prominent changes in cerebral function and structure, many of which differ from those found in the episodic type (17). It has been suggested that in some chronic patients central sensitization amplifies and becomes permanent (18), which is probably the reason why many preventive therapies lose efficacy.

Migraine is thus chiefly a central nervous system disorder. There is nonetheless some circumstantial evidence that the peripheral nervous system might play a causal or aggravating role in certain migraine patients. For instance, pericranial tenderness on palpation is well known in migraineurs (19). In 30% of patients palpation of scalp trigger points may provoke an attack (20). In one patient a migrainous headache was suggested to be due to compression of the lesser occipital nerve by a lymph node (21). It was recently shown that trigemino-vascular meningeal afferents project extracranially through the skull (22) and that activation of these extracranial afferents in rats causes release of calcitonin gene-related peptide (CGRP) from the dura, providing evidence that extracranial noxious signals may influence meningeal nociception (23). Despite the scarcity of data favoring a role for extracranial peripheral nerves in migraine, these nerves have been targeted by various therapeutic interventions.

## Management

The management of migraine patients includes acute interventions to alleviate the attack and preventive treatments aiming at a reduction of attack frequency and disability. Acute antimigraine drugs comprise nonsteroidal anti-inflammatory drugs (NSAIDs), simple or combined analgesics and specific antimigraine drugs like triptans and, in some countries, ergots. Analgesics and specific antimigraine drugs have a high propensity to chronify migraine when overused (24). Preventive drugs have limited efficacy (on average 50%). Many of them have cumbersome adverse effects (25) and they are likely to become progressively ineffective in chronic migraine (26) or medication-overuse headache (27).

Alternative treatments have been used for a long time, but they have received increasing attention recently, given the lack of new advances in pharmacotherapy.

We will focus here on interventions that are supposed to act on pericranial nerve branches.

Schematically they can be subdivided into neurostimulations, infiltrations/blocks, and surgical decompressions.

## Peripheral neurostimulation

Electrical stimulation of peripheral nerves (PNS) is an effective way to relieve pain within the territory of the stimulated nerve. It is possibly due to the activation of afferent A $\beta$  fibers and subsequent gate control mechanisms in the spinal cord dorsal horn or/and to the activation of descending supraspinal controls from periaqueductal gray and rostroventromedial medulla (28,29). PNS was initially used in chronic pain syndromes (30), thereafter in occipital neuralgia (31) and subsequently in migraine prevention (32). The modality of PNS was often chosen according to the migraine form, invasive—continuous and applied in the most severely disabled patients—or noninvasive—intermittent and applicable to all patients.

### Invasive PNS

Invasive PNS was explored as preventive therapy quasi-exclusively in patients suffering from drug-resistant chronic migraine.

**Occipital nerve stimulation (ONS).** The most studied technique is greater ONS. Besides small and/or heterogeneous open studies, three short-term (i.e. three months each) randomized, controlled trials (RCTs) were published (33–35). The Occipital Nerve Stimulation for the Treatment of Chronic Migraine Headache (ONSTIM) study ( $N=66$  patients) (34) showed a reduction of at least 50% in headache frequency and a decrease on the headache intensity scale in 39% of patients treated with active ONS during 12 weeks, whereas no improvement was found in the sham-stimulated or medically treated groups. However, ONSTIM was not powered to convincingly demonstrate effectiveness of ONS. In the sham-controlled Precision Implantable Stimulator for Migraine (PRISM) study (33), ONS did not produce any significant reduction in headache days in 125 patients with drug-resistant migraine with or without medication overuse. Finally, in the largest RCT of ONS in 157 patients with chronic migraine, no difference was found between sham and verum groups in the primary outcome measure (at least 50% reduction in mean daily headache intensity). However, a higher percentage of effectively stimulated patients achieved a 30% reduction in mean headache days ( $p<0.05$ ) and a decrease in migraine-related disability score (MIDAS) ( $p<0.01$ ); 51% of patients stated they

were satisfied with the treatment compared to 19% in the sham group (35). After the three-month randomized phase, patients continued an open-label phase of 40 weeks. Monthly headache days were significantly reduced by 6.7 days in the intention-to-treat group, and by 7.7 days in a group of patients with “intractable” chronic migraine ( $p < 0.01$ ) (36). In a recent small, randomized, crossover study of eight patients suffering from chronic migraine, suprathreshold stimulation was more effective than subthreshold stimulation, while the latter was superior to no stimulation (37).

These data suggest that ONS may be a promising treatment option for chronic migraine patients, but conclusive evidence from large RCTs is still missing. Moreover ONS can be associated with adverse effects and complications (local pain, intolerable paresthesias, local infection, electrode displacement, battery replacement) and the cost of the device is high (around 15,000–20,000 euros) while the clinical benefit seems modest (32).

In a retrospective open study of 44 patients with chronic migraine, the combination of ONS with supra-orbital nerve stimulation (SNS) was reported to reduce the frequency of severe headaches by 81% (38,39). Half the patients had nearly complete disappearance of headaches (mean follow-up 13 months) (40), which is an interesting result that needs to be confirmed in an RCT.

**Vagus nerve stimulation (VNS).** Invasive VNS has shown efficacy in refractory epilepsy. In a retrospective study of 10 implanted epilepsy patients suffering also from migraine, eight had at least a 50% reduction in headache frequency six months after starting VNS (40). Other observational VNS studies included small numbers of patients, but reported overall an improvement in 50% of patients (32).

### Non-invasive PNS

Compared to the invasive methods described above, noninvasive PNS can in theory be applied to any patient, including the less-disabled ones.

**Transcutaneous supraorbital nerve stimulation (tSNS).** The effectiveness of the portable tSNS Cefaly® for migraine prophylaxis has been recently evaluated in a randomized, double-blind sham-controlled trial (41). Sixty-seven episodic migraineurs were treated with daily tSNS or sham sessions of 20 minutes for three months. Compared to baseline, the mean monthly number of migraine days had significantly decreased after three months in the tSNS ( $6.94 \pm 3.04$

vs.  $4.88 \pm 3.46$ ;  $p < 0.05$ ), but not in the sham group ( $6.54 \pm 2.61$  vs.  $6.22 \pm 2.99$ ;  $p = \text{ns}$ ). The 50% responder rate was significantly greater in the tSNS (38.1%) than in the sham group (12.1%,  $p < 0.05$ ). Acute antimigraine drug intake was also significantly reduced in the verum but not in the sham group.

In an Internet survey of participants in the general population renting the tSNS Cefaly® device before deciding to buy it or not (42), a majority (54.4%) of 2313 individuals declared themselves satisfied and decided to keep the device (average testing period: 58.2 days). Among the unsatisfied patients (46.6%), the built-in monitoring system of the time the device was used showed poor compliance (tSNS used 48.6% of the recommended time, 4.46% of patients did not even switch the device on). Only 4.3% of individuals reported one or more adverse event(s) such as local pain/intolerance to paresthesia (2.03%), arousal changes (0.82%), and headache after the stimulation (0.52%). A transient local skin allergy was seen in 0.09%.

There is no RCT of this device for the abortive treatment of migraine attacks.

**Transcutaneous VNS.** New devices thought to stimulate the vagus nerve transcutaneously (tVNS) have recently been developed and their efficacy as acute and preventive treatments of primary headaches is being evaluated. Preliminary open data in 30 patients suggest that the Gammacore® device targeting the tVNS in the neck was effective in aborting migraine attacks, 21% of patients being pain free at two hours (43).

In a randomized, sham-controlled pilot study of chronic migraine patients (44), two months of three daily 90-second stimulations produced at least a 50% reduction in headache days in four out of 26 patients (15%), compared to none out of 23 in the sham-stimulated group. This modest beneficial effect was confirmed in the subsequent open-label phase (45), but further studies are clearly needed to determine the role of tVNS in migraine management. Besides neck muscle contractions in some patients, there were no significant adverse effects.

### Conclusion

Invasive ONS still awaits definitive proof of efficacy and could be envisaged only after failure or intolerance of several preventive antimigraine drugs in chronic migraine sufferers (46). In medication overuse headache patients, it is crucial to detoxify before considering any invasive neurostimulation, as drug overuse seems to be

associated with a less favorable outcome with ONS (47). Patients must be aware that outcome is uncertain, and that improvement may be moderate.

Noninvasive PNS, especially tSNS, can be proposed to less-disabled migraineurs as preventive or add-on migraine therapy (42). Although evidence of benefit is lacking, tSNS and tVNS could also be proposed as add-on to drug-resistant chronic migraine patients, before turning to more invasive and expensive devices (48).

Because of the paresthesias they produce, it is notoriously difficult to correctly blind PNS trials. Appropriate RCTs are mandatory, the more so that the placebo response is greater with devices than with oral drug therapies (49). More studies are needed to verify that subthreshold stimulations can be adequately used as controls and to establish dose-response curves (32,35).

The studies performed up to now with the noninvasive devices indicate that compliance may be the real challenge to solve in RCTs and in clinical practice (45).

### Infiltrations/blocks of pericranial nerves

Many studies have been performed in the past decades to evaluate the effects of infiltrations or “blocks” in the region of the greater occipital nerve (GON) in migraine, both as preventive or acute treatment. The rationale for such treatments is the anatomic-physiological convergence of C2 dermatoma and trigeminovascular afferents in the spinal trigeminal nucleus underlying referred pain from the neck and orbitofrontal regions innervated by the ophthalmic nerve (50).

The major studies are summarized in Table 1 (51–62). Unfortunately, there are very few controlled trials and no standardized methods were used for the selection of migraine patients (some had fixed unilateral headache, others not), the timing of infiltrations (ictal or interictal), the technique of infiltrations or blocks (unilateral or bilateral, association with blocks of other pericranial nerves or trigger point injections, one or more interventions), the compounds used for the blocks (local anesthetics alone or combined with different types and dosages of steroids) and particularly the evaluation of outcomes (number of headache-free days, variable percentage reduction of headache days or attacks, non-uniformly standardized pain indices). The great heterogeneity of published studies therefore renders their evaluation difficult.

Overall, a complete or partial beneficial preventive effect was reported in 48–100% of adult migraineurs, lasting from a few days to several months. A retrospective study also found partial benefit (<35%) from GON injections in pediatric chronic migraineurs (60). In one controlled, single-blinded study the addition of steroids for GON blocks was not superior to the anesthetic drug

alone (56). Similarly, in one recent placebo-controlled, randomized, double-blinded trial (61) comparing GON injections with 2.5 ml 0.5% bupivacaine plus 0.5 ml (20 mg) methylprednisolone to blocks with 2.75 ml normal saline plus 0.25 ml 1% lidocaine in episodic ( $n=54$ ) and chronic ( $n=9$ ) migraineurs (verum group  $n=33$ ; placebo group  $n=30$ ), the blocks with steroids showed no superiority over placebo.

By contrast, in another recent double-blind, placebo-controlled study of suboccipital blocks in 72 chronic migraine patients—available at present only in abstract form—comparing four weekly injections of saline to 0.5% bupivacaine (62), the number of headache days decreased from  $16.9 \pm 5.7$  days to  $13.2 \pm 6.7$  days in the former ( $p=0.035$ ) but from  $18.1 \pm 5.3$  days to  $8.8 \pm 4.8$  days ( $p<0.001$ ) in the latter, and the superior effect of bupivacaine was confirmed in an open two-month extension study. Medication overuse tripled the risk of failure of the treatment in one study (58) but had no influence on outcome in two other ones (55,59). In many studies palpation tenderness in the GON region was taken intuitively as a criterion for selecting patients for GON blockade/infiltration. The positive predictive value of GON tenderness was assessed in two independent studies with divergent results: It was associated with better outcome in the first (55), but not in the second (59).

GON blocks were also tested as a symptomatic treatment for acute migraine headache. Combined lidocaine blockade of GON and supraorbital (SO) nerves in 14 patients produced only negligible pain reduction (6%) after 30 minutes; 50% of patients did not respond at all (63). By contrast, in an open study of 25 patients with unilateral migraine (11 episodic and 14 chronic) and brush allodynia, a GON block with 1 cc of a 50/50 mixture of 2% lidocaine and 0.5% bupivacaine reduced headache intensity by a mean of 46.8% in 89.5% of patients after 20 minutes and ipsilateral allodynia by a mean of 65.7% in all patients (64). The same procedure reduced the pain and allodynia scores respectively by 64% and 75% after five minutes (65). The mean duration of benefit in these studies was four days, both in episodic and chronic migraineurs. In a case report, a woman affected by basilar migraine underwent GON infiltration with 3 ml of 0.25% bupivacaine and 1 ml of 40 mg/ml triamcinolone and reported after a few minutes partial resolution of the aura symptoms and complete disappearance of the headache (66).

It is difficult to assess whether SO nerve blocks are effective, as they have rarely been studied in isolation. In the study by Bovim and Sand (1992) (63), the combination of GON and SO nerve blocks with 0.5–1.5 ml of lidocaine (20 mg/ml and 12.5  $\mu$ g /ml adrenaline) was not effective. By contrast, in another study comparing SO and GON blocks alone and the combination of

**Table 1.** Preventive effects of GON blocks in migraine.

Authors	Type of study	Number of migraine patients	Unilateral/bilateral headache	Unilateral/bilateral treatment	Number of treatments	Medications used	% of ameliorated patients ( $\geq 30\%$ improvement or pain free)	Adverse effects (% patients if available)
Saadah and Taylor 1987 (51)	Prospective uncontrolled	112 UH (occipital tenderness)	Bilateral	Bilateral	1–9	10 cc 1% lidocaine + 2 cc betamethasone mixture	56%	Dizziness Soreness at injection site
Anthony 1992 (52)	Prospective controlled unblinded	50 M (+“GON irritation”) ictally 20 M +“GON irritation” interictally	Unilateral (fixed)	Unilateral	1	4 ml 1% lignocaine +160 mg methylprednisolone acetate GON (ictal) 4 ml 1% lignocaine + 160 mg methylprednisolone acetate i.m. (interictal)	88% (“headache-free from 10 to 66 days”)	No
Gawel and Rothbart 1992 (53)	Retrospective	97 M	?	?	1 or multiple	Methylprednisolone acetate + xylocaine	53.6% (“significantly better”)	?
Caputi and Firetto 1997 (54)	Prospective uncontrolled	7 EM 4 CM	2 Unilateral (fixed) 6 Unilateral (shifting) 3 Bilateral	5 Bilateral 6 Unilateral (combined with supraorbital block)	5–10	0.5–1 ml of 0.5% bupivacaine	63.6%	No
Afridi et al. 2006 (55)	Prospective	54 CM (31 MOH)	?	Unilateral	1	3 ml of mixture of lidocaine 2%+80 mg methylprednisolone	48.15%	Dizziness Alopecia Headache (3.7%)
Ashkenazi et al. 2008 (56)	Prospective, placebo-controlled, single-blinded	37 TM (20 MOH)	?	Bilateral (plus 12 “trigger points”)	1	0.9 ml lidocaine 2% + 0.9 ml bupivacaine 0.5% + 0.2 ml saline (placebo) or 0.9 ml lidocaine 2% + 0.9 ml bupivacaine 0.5% + 0.2 ml triamcinolone 40 mg/ml (verum)	Acute pain relief Headache free for 2.7 $\pm$ 3.8 days (placebo) or 1 $\pm$ 1.1 days (verum) No difference between the two groups	No
Takmaz et al. 2008 (57)	Prospective	8 EM 2 CM	?	?	3–5	1.5 ml of 0.5% bupivacaine	100% (?)	Vaso-vagal syncopal attack (1%)
Tobin and Flitman 2009 (58)	Retrospective	57 M (10 MOH)	?	?	1	1.5 ml of 0.5% bupivacaine +60 mg methylprednisolone acetate	71.2% (?)	?

(continued)



Table 1. Continued.

Authors	Type of study	Number of migraine patients	Unilateral/bilateral headache	Unilateral/bilateral treatment	Number of treatments	Medications used	% of ameliorated patients ( $\geq 30\%$ improvement or pain free)	Adverse effects (% patients if available)
Weibelt et al. 2010 (59)	Prospective	150 CM (72 MOH)	?	102 Bilateral 48 Unilateral	I	10 cc bupivacaine and 20 mg triamcinolone	52%	Vaso-vagal presyncope (14%) Hypophonia and dysphagia (2%) Lightheadedness Local soreness Tingling/numbness in the nerve distribution
Gelfand et al. 2014 (60)	Retrospective	29 CM (<18 years)	?	Unilateral	I	80 mg methylprednisolone acetate +20 mg 2% lidocaine (half dosage in children weighing < 40 kg)	35%	Injection site pain (12%) Abdominal distension (3%) Fat redistribution (3%) Injection site paresthesia (3%) Neuralgia (3%) Weight increase (3%)
Dilli et al. 2014 (61)	Prospective, randomized, placebo-controlled, double-blinded	54 EM and 9 CM (30 placebo + 33 verum)	Unilateral (7 verum and 7 placebo) Bilateral (26 verum and 23 placebo)	Unilateral (7 verum and 7 placebo) Bilateral (26 verum and 23 placebo)	I	0.25 ml lidocaine 1% + 2.75 ml saline (placebo) 2.5 ml bupivacaine 0.5% +0.5 ml methylprednisolone 40 mg/ml (verum)	( $\geq 50\%$ responders) placebo: 30% verum: 30%	Injection site pain (12%) Abdominal distension (3%) Fat redistribution (3%) Injection site paresthesia (3%) Neuralgia (3%) Weight increase (3%)
Inan et al. 2014 (62)	Prospective, randomized, placebo-controlled, double-blinded	72 CM (33 placebo + 39 verum)	?	?	4	2.5 ml saline (placebo) 1.5 ml of 0.5% bupivacaine + 1 ml saline (verum)	↑21.9% headache-free days after one month ↑51.4% headache-free days after one month	(21%): local pain, vertigo, back pain, cervical neck spasm (25.6%): local pain, vertigo, nausea

GON: greater occipital nerve; M: migraine – type nonspecified; EM: episodic migraine; CM: chronic migraine; TM: transformed migraine (according to Silberstein et al 2004); UH: unspecified headache; MOH: medication-overuse headache; i.m.: intramuscularly; SN: supraorbital nerve; ?; data not available.

both, after SO blocks solely (54) a 50% improvement of headache frequency was found in 68.75% of patients after one month and in 75% of patients after six months. Recently, three consecutive bilateral SO and infraorbital nerve blocks with 1.5 ml of 1% lidocaine in episodic migraine patients were reported to significantly reduce mean headache frequency and MIDAS score (67).

To conclude, although infiltrations with steroids and anesthetic blocks of cranial nerves have been extensively used in migraine patients for a long time and effectiveness was reported in many observational studies, there are only two RCTs available: in one of them, comparing saline to bupivacaine in chronic migraine (62), the effect of bupivacaine exceeds that of placebo, but in the other, where bupivacaine plus methylprednisolone was compared to saline plus lidocaine, both groups had similar outcomes. Adverse effects reported after peripheral nerve blocks are rare and minor (see Table 1). Further studies are needed to determine in which subgroups of migraine patients suboccipital or SO nerve blocks are superior to placebo.

## Surgical decompressions

As mentioned above, there is scarce evidence that nervous structures in the pericranium or face play a primary causative role in migraine pathogenesis. Many patients nevertheless refer their pain to the surface of the head or neck in close anatomical relationship with branches of pericranial nerves. Although these superficial pain locations are nowadays merely attributed to referred pain from the visceral part of the ophthalmic nerve, surgical attempts to treat migraine by acting directly on cranial nerves have been published as case reports as early as the first half of the 20th century (68).

More recently, decompression of pericranial nerves by sectioning neighboring muscles and sections of superficial nerve branches were proposed as therapeutic options for migraine patients. The bulk of data concerning these procedures originates from Guyuron's group in Cleveland (see Table 2) (69–81). These authors first studied retrospectively patients who underwent resection of *corrugator supercilii* muscle for rejuvenation and reported improving or disappearance of their headaches (69). This was followed by a prospective study on 29 patients with hypertrophy of the *corrugator supercilii* muscle and at least 50% amelioration by one injection of 25 U of botulinum toxin type A into this muscle (70). Twenty-four patients out of 29 responded to botulinum toxin, 16 having complete disappearance of headaches, and eight partial improvements. The complete responders underwent a *corrugator supercilii* muscle resection while the others had in addition a transection of the

zygomaticotemporal branch of the trigeminal nerve and repositioning of the temple soft tissues. After follow-up (222–494 days), all patients except one improved; 10 out of 22 operated patients were pain free. Assuming that various pericranial trigger sites might play a role in migraine and that they can be identified by local botulinum toxin injections, the same group in a subsequent unblinded prospective study (71) allocated patients to one of a combination of four surgical techniques and followed a nonoperated on control group of 25 patients for one year. Depending on the origin of pain and botulinum toxin effect, the surgical procedures were 1) removal of *corrugator supercilii*, *depressor supercilii* and *procerus* muscles (90% of patients); 2) endoscopic removal of 3 cm of the zygomaticotemporal branch of the trigeminal nerve (80%); 3) resection of the *semispinalis capitis* muscle and shielding of the greater occipital nerve (38%); 4) septoplasty and inferior and/or middle turbinectomies (70%). Ninety-two percent of the operated patients were reported to have at least 50% reduction in migraine headache frequency and duration, while only 15.8% of controls improved. There was also a significant effect on quality of life, work loss and cost for migraine care in the operated group.

In the five-year follow-up of the patients included in this study (75), out of 69 patients who completed it without re-interventions, six were operated at one site, 15 at two, 30 at three and 18 at all four trigger sites. Eighty-eight percent of patients reported beneficial effects from the surgical treatment at the end of the five-year follow-up: disappearance of headache in 29%, a  $\geq 50\%$  reduction in 59%.

In the only sham-controlled study (74), 130 patients with “frequent moderate to severe migraine” with or without aura were included on the basis that they reported a so-called “trigger site,” i.e. a predominant site “where the migraine headache begins and settles and corresponds to the anatomical zone of potential irritation of the trigeminal nerve.” Among them, 75 were included in the study because they had at least 50% amelioration after injection of 25 U botulinum toxin into the “trigger” area and completed a one-year follow-up. They were divided into three groups according to the localization of the “trigger” site: frontal, temporal or occipital. The “frontal” group underwent the above-mentioned procedure 1, the “temporal” group procedure 2, and the “occipital” group procedure 3. In each group a third of patients underwent a sham operation. In the verum arm ( $n = 49$ ) 83.7% of participants from the three groups reported a significant amelioration or elimination of headaches, whereas in the sham arm ( $n = 26$ ) 57.7% had a similar positive outcome.

More recently, the same group published several retrospective studies aiming at identifying predictors

**Table 2.** Effect of surgical decompression of pericranial nerves in migraine.

Authors	Type of study	Inclusion criteria of migraine patients	Number of patients selected for surgery (enrolled)	Selection criteria for surgery	Surgery protocols	Duration of follow-up (months)	% of patients with favorable outcome ( $\geq 50\%$ improvement/pain free)	Adverse effect (% patients)
<sup>a</sup> Guyuron et al. 2000 (69)	Retrospective	Telephone interview; ICHD-I criteria	39 total 29 MO 10 MA (249)		<i>Corrugator supercilii</i> muscle resection	5–122	79.5 (61.5/38.5)	None?
<sup>a</sup> Guyuron et al. 2002 (70)	Prospective	ICHD-I criteria by neurologists + corrugator hypertrophy	24 (29)	At least 50% amelioration with 25 UI BTA injection into the CSM	CSM resection (all patients) + ZTTN transection (6 patients)	7.5–16.5	95.5 (50/45)	Temporary numbness in the temple area (100%)
<sup>a</sup> Guyuron et al. 2005 (71)	Prospective	ICHD-I criteria by neurologists	89 (125: among them 25 nonoperated on (control group))	At least 50% amelioration after 25 UI BTA	Combinations of: GMG removal (frontal TS) ZTTN transection (temporal TS) SSCM removal (occipital TS) Septoplasty+inferior/middle turbinectomy (nasal TS)	I and 12	92% (57/35)	Nasal dryness Rhinorrhea Recurrence septal deviation Itching Hair loss Intraoperative bleeding Neck stiffness Epistaxis Sinus infection Hematoma Bleeding
Dirnberger and Becker 2004 (72)	Prospective	ICHD-I criteria by neurologists	60 (60) 33 EM 13 CM 14 MOH	None	CSM resection + corrugator and depressor muscle resection	6	58.3% (!?)	
Poggi et al. 2008 (73)	Retrospective	ICHD-II criteria by neurologist (6 patients with additional diagnosis of CH and TTH)	18 (18)	$\geq 50\%$ amelioration after 12.5 UI BT A	Combinations of: GMG removal ZTTN transection SSCM removal	6–41	88.9 (72.2/16.7)	?
<sup>a</sup> Guyuron et al. 2009 (74)	Sham-controlled	ICHD-II criteria by neurologist	75 (130–317?) 49 verum 26 sham	$\geq 50\%$ amelioration after 25 UI BTA injection into each TS	Verum: Combinations of: GMG removal (frontal TS) ZTTN transection (temporal TS) SSCM removal (occipital TS) Sham:	12	Verum: 83.7 (26.6/57.1) Sham: 57.7 (53.9/3.8) (significantly different)	Numbness Temporal hollowing Temporary itching Uneven brow movement Hair loss Residual CSM

(continued)



**Table 2.** Continued.

Authors	Type of study	Inclusion criteria of migraine patients	Number of patients selected for surgery (enrolled)	Selection criteria for surgery	Surgery protocols	Duration of follow-up (months)	% of patients with favorable outcome ( $\geq 50\%$ improvement/ pain free)	Adverse effect (% patients)
<sup>a</sup> Guyuron et al. 2011 (75)	Prospective (follow-up of Guyuron et al. 2005)	ICHD-I criteria by neurologists	79 (125; among them 25 non-operated (control group) 59 MO 14 MA 6 MO + MA	AI least 50% amelioration with 25 UI BTA injection into each TS	Exposure of the same muscles and nerves maintaining their integrity Combinations of: GMG removal (frontal TS) (92.8%) ZTTN transection (temporal TS) (84%) SSCM removal (occipital TS) (36.2%) Septoplasty+inferior/middle turbinectomy (nasal TS) (73.9%)	60	88.4 (59.4/29)	Temporal nerve injury Neck stiffness Neck weakness Skin numbness Hypersensitivity Hyposensitivity
<sup>a</sup> Larson et al. 2011 (76)	Retrospective	ICHD-? criteria by neurologists	382 (167)	BTA as above <sup>a</sup>	Combinations of: GMG removal (frontal TS) ZTTN transection (temporal TS) Septoplasty+inferior/middle turbinectomy (nasal TS) SSCM removal (occipital TS) CSM transection	>11	79.6 (40.1/39.5)	?
De Ru et al. 2011 (77)	Retrospective	?	10 (10)	$\geq 50\%$ amelioration after 12.5 UI BTA		4-30	90 (!?)	Numbness (30%) Paresthesia (10%) Hematoma (10%) ?
<sup>a</sup> Liu et al. 2012 (78)	Retrospective	ICHD-? criteria by neurologists	335 (335) 245 = "group A": diagnostic BT injections at trigger site 90 = "group B": no BT or BT for therapeutic purposes	BTA as above <sup>a</sup> or none	Combinations of: GMG removal (frontal TS) ZTTN transection (temporal TS) Septoplasty+inferior/middle turbinectomy (nasal TS)	12	Group A: 84.5 (48.2/36.3) Group B: 80.0 (47.8/32.2) (not significantly different)	?

(continued)

Table 2. Continued.

Authors	Type of study	Inclusion criteria of migraine patients	Number of patients selected for surgery (enrolled)	Selection criteria for surgery	Surgery protocols	Duration of follow-up (months)	% of patients with favorable outcome ( $\geq 50\%$ improvement/ pain free)	Adverse effect (% patients)
<sup>a</sup> Chepla et al. 2012 (79)	Retrospective	ICHD- $\gamma$ criteria by neurologists	86 (86) 43 = Group M: GMG resection 43 = Group MF: GMG resection + supraorbital foraminotomy	BTA as above <sup>a</sup> ?	SSCM removal (occipital TS) GMG removal OR GMG removal plus supraorbital foraminotomy (in both groups: plus combination of ZTTN transection, septoplasty+inferior/middle turbinectomy, SSCM removal)	12	100? (?!) Significantly reduced headache frequency and severity and in forehead pain in group MF	?
<sup>a</sup> Lee et al. 2013 (80)	Retrospective	ICHD- $\gamma$ criteria by neurologists	188 (188) 144 "BTA success group": at least 50% amelioration with BT injection 44 "BT failure group": less than 50% amelioration with BT injection	BTA as above <sup>a</sup> ?	Combinations of: GMG removal (frontal TS) ZTTN transection (temporal TS) Septoplasty+inferior/middle turbinectomy (nasal TS) SSCM removal (occipital TS)	> 12	BTA success group: 90.3 (53.5/36.8) BTA failure group: 72.7 (45.4/27.3) (significantly different)	?
<sup>a</sup> Chmielewski et al. 2013 (81)	Retrospective	ICHD- $\gamma$ criteria by neurologists	170 (170) 115 "control": SSCM removal 55 "Occipital artery resection": SSCM removal plus occipital artery resection	?	SSCM removal (occipital TS) or SSCM removal (occipital TS) plus occipital artery resection	12-87	Control group: 91.3 (27.0/64.3) Occipital artery resection group: 80.0 (41.8/38.2) (significantly different)	?

<sup>a</sup>Studies performed by the same group (possible overlap of cases).

BTA: botulinum toxin type A; CSM: *corrugator supercilii* muscle; GMG: glabellar muscle group; ZTTN: zygomatico-temporal branch of trigeminal nerve; SSCM: *semispinalis capitis* muscle; TS: trigger site; MO: migraine without aura; MA: migraine with aura; EM: episodic migraine; CM: chronic migraine; ICHD: International Classification of Headache Disorders; MOH: medication-overuse headache; CH: cluster headache; TTH: tension-type headache; ? : data not available.

of favorable outcome (76,78,80) or added value of additional surgical procedures like supraorbital foraminotomy (79) or ligation of the occipital artery (81).

Only three other groups have published retrospective studies on the effects of surgery in the frontal area in migraine. In the largest study (72) resection of the *corrugator* and *depressor muscles* in 60 episodic or chronic migraineurs, a  $\geq 50\%$  reduction in headache days at a six-month-follow-up was found in 58.3% of patients, most of them having a mild form of migraine. In another study (73) 16 out of 18 migraine patients responding to botulinum toxin and operated on at multiple sites in various combinations had a  $\geq 50\%$  amelioration of migraine headaches at a mean follow-up of 16 months. In 10 patients suffering from frontally located “chronic daily headache” (77) and ameliorated by  $\geq 50\%$  after at least two frontal injections of botulinum toxin, nine had  $\geq 50\%$  improvement after *corrugator* muscle resection.

The rationale for surgical decompression of pericranial nerves in migraine is that compression of peripheral nerves induces inflammation and peptide release that may reach the meninges and hence trigger migraine headaches. Though still speculative, this rationale may gain support from recent studies demonstrating extracranial projections of meningeal afferents (22).

One weakness of peripheral nerve decompressions is that the evidence comes from retrospective or prospective uncontrolled studies with only one exception. The migraine patients included in these studies all had some uncommon clinical characteristics (82), such as strictly localized and side-locked headache and the presence of “trigger sites” that are more typical of cranial neuralgias and tension-type headaches (4). Also, the “constellation of symptoms” by which the authors classify patients in order to operate on specific sites are common to other primary or secondary headaches like neuralgias, headaches attributed to temporomandibular dysfunction, chronic tension-type headache, chronic/recurrent rhinosinusitis, mucosal contact points or concha bullosa, and whiplash. Many of these head pains may coexist with and/or aggravate migraine and their alleviation could indirectly cause clinical improvement in migraineurs.

Another puzzling observation in published studies concerns the selection of patients. Most of them were diagnosed as episodic migraineurs. Botulinum toxin type A injections at “trigger sites” reduced headache frequency by at least 50% in 58% and 90% of patients (70,71,74,75), which clearly contrasts with the much lower responder rate (maximum 30%, not significantly different from placebo) in RCTs of botulinum toxin in episodic migraine (83). As the placebo response has been very high in all botulinum toxin trials (84,85), this may have favored the selection of placebo responders.

In the sole sham-controlled study of peripheral nerve decompression, the placebo response was particularly high (58%), possibly because of the possibility that the incision and the undermining of pericranial tissues may have altered neurosensory functions and that some patients may have exaggerated their preoperative symptoms to increase their chance of selection for surgery (70,71,74,77). In fact, the placebo response is in general higher with invasive than with drug treatments (49). The resulting therapeutic gain of  $\pm 25\%$  may appear clinically useful in very disabled patients, but in most published decompression studies there is no information about concomitant or previous preventive drug treatments or refractoriness to them.

Because of these confounding and atypical features surgical decompression of PNS cannot be considered as an established treatment option for migraineurs in general, although it may be useful in a subgroup of patients after careful weighing of possible side effects (see Table 2) and cost. Independent sham-controlled studies coming from different research groups and using standardized procedures for patient selection are warranted, including comparisons with optimized medical therapy.

## Conclusions

Acting on pericranial nerve branches to treat migraine is not novel. Although current knowledge of migraine pathophysiology favors a central nervous system dysfunction (12), there is some evidence that interventions targeting PNS are able to modulate neuronal circuits involved in central sensitization and pain control. Invasive or noninvasive neurostimulation, anesthetic/steroid blocks, and surgical decompression of pericranial nerves may act in this way, which suggests that their effect is merely symptomatic.

Advances in this therapeutic area will come from a better knowledge of migraine pathophysiology, more precise phenotyping of patients and advances in technology and treatment protocols. Larger, better-designed and comparative trials are needed to appraise the respective advantages, disadvantages and indications of most interventions discussed here. Such trials may be difficult to set up for treatments like nerve blocks for which there is no commercial interest.

The challenge will be to use comparable standards for the evaluation of their effects in drug trials and to manage adequately the blinding caveat.

## Literature search methods

English-language publications were searched for in PubMed up to July 2014, and updated in December 2014.

The following search terms were used: “migraine neurostimulation,” “migraine neuromodulation,” “migraine injection,” “migraine nerve infiltrations,” “migraine nerve blocks,” “migraine surgery” and “migraine decompression.” All the identified publications were individually assessed according to their

relevance to the topic. Specific exclusion criteria included: publications on single case reports, editorials and other review articles unless of exceptional importance. The reference lists of identified publications were also scrutinized for further relevant publications.

### Clinical implications

- The definitive evidence that percutaneous occipital nerve stimulation (ONS) is effective in chronic migraine has not been obtained yet, but some randomized controlled trials (RCTs) indicate nonetheless that ONS might ameliorate a subgroup of patients.
- Noninvasive transcutaneous supraorbital neurostimulation is superior to sham stimulation for the prevention of episodic migraine, and noninvasive vagus nerve stimulation in the neck is promising for chronic migraine. Technological advances and improved stimulation protocols may improve performance of these methods in the near future. Further study results are eagerly awaited.
- Since it is inexpensive and safe and there are some indications from observational studies for its usefulness, suboccipital infiltration may be an add-on option in selected patients, in particular those with fixed unilateral headaches and ipsilateral autonomic symptoms. Convincing evidence for efficacy from RCTs is, however, missing.
- Surgical decompression of pericranial nerves was found superior to sham surgery in one study and most published case reports are from the same group. Because of the heterogeneity of patients included, selection bias and the questionable inclusion criteria, the efficacy and usefulness of surgical decompressions in migraine patients cannot be considered as definitely established until other RCTs from other independent groups confirm it.

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### Conflict of interest

A.A., C.D.A. and D.M. have nothing to declare. J.S. is an advisor for Cefaly-Technology, St Jude Medical, ATI, Medtronic, AMGEN and Gedeon Richter.

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