Neuromodulation in Primary Headaches

Primary headaches represent a major burden, not only to patients but also to national health care systems in terms of socioeconomic consequences. Migraine incurs yearly costs of up to US$20 billion in the United States and up to US$27 billion in Europe. Patients with chronic primary headache have even greater impairment and generate more direct costs per capita than those with episodic forms. Patients with episodic cluster headache generated annual expenses of €1819 in a German sample, while those with the chronic form generated costs of €9073 per capita. Although most patients benefit from a range of acute and preventive drugs, a subgroup of patients remain refractory to treatment. For these patients, invasive techniques should be considered.

Nerve blocks with either local anesthetics or steroids (or combinations of both) provide only temporary relief in most patients

Despite good efficacy in some forms of primary headache, nerve blocks with either local anesthetics or steroids (or combinations of both) provide only temporary relief in most patients. Ablative procedures have been used widely for headaches, targeting both the peripheral nerves (such as neuroectomies, ganglionectomies, rhi- zotomies, injection of phenol or glycerol, radiofrequency ablation, or radiosurgery) and the central nervous system (such as trigeminal tractotomies or nucleotomies, mesencephalotomies, and thalamotomies). In the past 20 years, neuromodulatory approaches previously established in other intractable painful conditions have been used increasingly for refractory primary headaches. They have the advantage of being nondestructive, often minimally invasive, adjustable (in case of changes during the course of the disease), and in most cases reversible. Neuromodulatory approaches can be pragmatically classified according to implantation site (peripheral versus central nervous system) and invasiveness (noninvasive versus invasive approaches) (Table I).

Basic Concepts

Given that complex networks of pain-processing structures are activated and deactivated upon stimulation of a single target, “neuromodulation” is the more precise and neutral term compared to “neurostimulation,” which infers activation only. The mode of action differs substantially between different approaches. Peripheral stimulation can exert direct effects on the nerve such as a frequency-dependent conduction block. Segmental effects, as proposed by Melzack and Wall in their gate control theory, are an additional mechanism. Afferent sensory Aβ fibers block segmental transmission of
nociceptive input from Aδ and C fibers. As a peculiarity of the cranial region, occipital and trigeminal nociceptive afferent neurons converge onto interneurons in the trigeminocervical complex extending from the trigeminal nucleus caudalis to the upper cervical cord. This anatomical arrangement explains spreading of cervical pain to the frontal region or vice versa, which frequently occurs in primary headaches. Additionally, activation of ascending second-order neurons could modulate regions such as the periaqueductal gray to cause a successive activation of descending antinociceptive pathways, resulting in a net reduction of pain. Vagal nerve stimulation was recently shown to suppress activity in the trigeminal spinal nucleus elicited by nociceptive dural stimulation.

Central approaches convey their effects by top-down modulation, whereas peripheral approaches primarily rely on local or segmental and bottom-up mechanisms

Central neurmodulatory approaches mostly involve the top-down modulation of an intricate network of brain areas involved in nociceptive processing and antinociception upon stimulation of the target region, as shown for motor cortex stimulation. In a positron emission tomography (PET) study on the effects of deep brain stimulation (DBS) of the posterior hypothalamus, large parts of the so-called “pain matrix” were modulated, along with the hypothalamic gray ipsilateral to the stimulation electrode and the ipsilateral trigeminal nucleus and ganglion. On the basis of these PET findings, together with the observation that clinical effects can be delayed by several weeks to months, complex neuroplastic changes were proposed to be the principles underlying the effects of hypothalamic DBS.

Thus, central approaches convey their effects by top-down modulation, whereas peripheral approaches primarily rely on local or segmental and bottom-up mechanisms.

Patient Selection: Who and When?

The first step should be to confirm the correct diagnosis according to the current International Classification of Headache Disorders, 2nd edition (ICHD-II), diagnostic criteria. Then, the clinician should ascertain that the headache is in fact chronic, with (near) daily attacks, and that it is eventually refractory to the established pharmacotherapy (Table II). If these preconditions apply, a set of inclusion criteria for invasive neurmodulatory approaches should be met (see Table III).

Definition of Refractory Headache

Patients eligible for an invasive neurmodulatory approach should be refractory to the established local first- and second-line pharmacotherapy (refer to Table II for detailed information). Although not included in the above recommendations, combinations of these drugs may be required in some countries. Intracranial headaches imply psychosocial disability, which should be substantiated by adequate tests, such as the Migraine Disability Assessment (MIDAS) or Headache Impact Test (HIT-6). For more infrequent headaches, no specific criteria have been defined, and refractoriness can be assumed when established treatment according to the local guidelines is not effective.

Patients eligible for an invasive neurmodulatory approach should be refractory to the established local first- and second-line pharmacotherapy

Although occipital nerve blocks are not predictive of a favorable outcome in occipital nerve stimulation (ONS), several studies suggest that such blocks may have efficacy as a preventive

| Table I
| Summary of different neurmodulatory approaches |
| Peripheral | Central |
| Non-invasive | Transcutaneous electrical nerve stimulation (Transcutaneous vagal and supraorbital nerve stimulation) | Transcranial magnetic stimulation |
| | | Transcranial direct current stimulation |
| Invasive | Peripheral nerve stimulation | Deep brain stimulation |
| | Vaginal nerve stimulation | Spinal cord stimulation |
| | | Motor cortex stimulation |

| Table II
| Criteria for refractory primary headache |
| General: |
| • ICHD-II criteria are met. |
| • Significant interference with function or quality of life despite modification of triggers and lifestyle factors. |
| • Failure with adequate trials of preventative medication, alone or in combination. Failure is defined as no therapeutic effect or an unsatisfactory effect, intolerable side effects, or contraindication to use. Adequate is defined as an appropriate dose and appropriate length of time. |
| • Consideration of medication overuse. |
| Chronic Migraine: |
| 1. Failure with adequate trials (2 months at an effective dose) of preventive medicines, alone or in combination, from at least 2 of 4 drug classes: |
| a. Beta blockers |
| b. Anticonvulsants |
| c. Tricyclics |
| d. Calcium channel blockers |
| Chronic Cluster Headache: |
| Failure of at least four classes (where two should come from 1–3): |
| 1. Verapamil |
| 2. Lithium |
| 3. Methysergide |
| 4. Melatonin |
| 5. Topiramate |
| 6. Gabapentin |

Source: Modified according to Goadsby et al. and Schulman et al.
treatment. Therefore, occipital nerve blocks should be tried in patients with trigeminal autonomic cephalalgias and occipital neuralgias before an invasive approach. Botulinum toxin A has shown prophylactic efficacy when given by injection into the craniovertebral muscles in patients with chronic migraine, and so it should also be considered before an invasive approach in patients with chronic migraine.

It seems inappropriate to demand the use of noninvasive neuromodulation, either alone or as an add-on therapy, before a headache is classified as intractable

The role of noninvasive neuromodulation has not yet been fully examined. Single-pulse occipital transcranial magnetic stimulation (TMS) was more effective than sham treatment in aborting acute attacks in patients with migraine if given within 1 hour after the beginning of the aura. However, TMS was less effective than triptans, and its benefits were examined only in patients with aura; thus, further studies are needed to fully explore its therapeutic potential. Transcranial electric nerve stimulation (TENS) was only found to be effective if combined with other electrical stimulation paradigms in patients with migraine and tension-type headache and in combination with physical therapy in patients with tension-type headache, according to a Cochrane review. Effects of transcranial direct current stimulation (tDCS) have only been reported in a small case series on various primary headaches and in a small sham-controlled study in patients with chronic migraine. At present, it therefore seems inappropriate to demand the use of noninvasive neuromodulation, either alone or as an add-on therapy, before a headache is classified as intractable.

Further Selection Criteria for Neuromodulation

The criteria for patient selection shown in Table III are based upon those published for selection of patients with chronic cluster headache for hypothalamic DBS. As chronic primary headaches tend to fluctuate over time and even remit temporarily, a history of 2 years has been proposed, as documented in patient diaries.

Overuse of analgesics and triptans is a frequent cause of chronification in primary headaches and is a reversible condition. Additionally, medication overuse is associated with a worse outcome in migraine patients receiving ONS. Therefore, candidates with overuse should withdraw from abortive drugs before any invasive treatment is considered.

Overuse of analgesics and triptans is a frequent cause of chronification in primary headaches and is a reversible condition

Psychiatric comorbidity (especially affective and anxiety disorders) can frequently be found in patients with severe impairment and does not necessarily lead to exclusion. However, caution should be exercised in patients with personality or somatoform disorders.

<table>
<thead>
<tr>
<th>Table III</th>
<th>Criteria for invasive neuromodulatory approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic primary headache with a documented history of 2 years</td>
<td></td>
</tr>
<tr>
<td>Chronic headache with (near) daily pain recorded in a headache diary and significant psychosocial impairment</td>
<td></td>
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<tr>
<td>Refractory to established pharmacotherapy (see Table II)</td>
<td></td>
</tr>
<tr>
<td>Attacks have been side-locked for the last 12 months in unilateral headaches scheduled for unilateral stimulation (such as DBS)</td>
<td></td>
</tr>
<tr>
<td>Normal neurological examination (except for symptoms typical of the underlying headache, such as Horner’s syndrome in cluster headache)</td>
<td></td>
</tr>
<tr>
<td>Unremarkable MRI of the brain, including the craniovertebral junction, and arterial and venous MR angiography of the intracranial vessels</td>
<td></td>
</tr>
<tr>
<td>Medication overuse of analgesics or triptans has been considered</td>
<td></td>
</tr>
<tr>
<td>No personality or somatoform disorder, and no addictive disorder</td>
<td></td>
</tr>
<tr>
<td>No other implanted biomedical stimulator</td>
<td></td>
</tr>
<tr>
<td>No inadequately high risk for anesthesia</td>
<td></td>
</tr>
<tr>
<td>No other relevant medical condition (such as coagulopathy)</td>
<td></td>
</tr>
<tr>
<td>Neurosurgical team with experience in invasive neuromodulation</td>
<td></td>
</tr>
<tr>
<td>Experienced pain center responsible for patient selection and follow-up after implantation</td>
<td></td>
</tr>
<tr>
<td>Not pregnant</td>
<td></td>
</tr>
<tr>
<td>Written informed consent</td>
<td></td>
</tr>
</tbody>
</table>

Source: Modified according to Leone et al.10
Abbreviations: DBS, deep brain stimulation; MRI, magnetic resonance imaging.

Peripheral Approaches

Occipital Nerve Stimulation

Occipital Neuralgia

Occipital neuralgia was the first indication for which ONS was tried, with a response rate of 100%. However, the diagnosis was later changed to chronic migraine in most of the patients from the initial publication. In successive studies, clinical efficacy was later ascertained in two case series, with a reduction in the number of attacks of at least 50% in 9 out of 9 patients (100%) and 8 out of 11 patients (73%). Occipital neuralgia is rare, and it usually responds to antiepileptic medication and occipital nerve blocks, so that intractable forms are exceptional.

Migraine

In two larger case series with 10 and 25 patients with “transformed” migraine (more than 15 headache days per month in patients fulfilling the International Headache Society criteria for episodic migraine), up to 88% had at least a 50% reduction of attack frequency or headache severity, with a mean follow-up of 18 months in the latter series. MIDAS scores improved significantly by an average of 89%.

However, two larger multicenter randomized, sham-controlled studies have been conducted with ambiguous results. The
PRISM (precision implantable stimulator for migraine) study has only been presented in preliminary form.\textsuperscript{13} Patients with intractable chronic and episodic migraine according to the ICHD-2 criteria\textsuperscript{1} (n = 125) received either 12 weeks of bilateral active or sham stimulation after receiving external stimulation for 5 to 10 days. The primary endpoint, reduction of number of headache days per month, was not met after the blinded period, with a reduction of 5.5 days in the active and 3.9 days in the sham group. A subgroup analysis revealed that patients with medication overuse (particularly opioids) had a less favorable outcome, raising the question as to whether the study could have been underpowered.

The multicenter, randomized, sham-controlled ONSTIM (occipital nerve stimulation for the treatment of intractable chronic migraine headache) study included only patients with chronic migraine according to the ICHD-2 criteria who had responded to an occipital nerve block, did not overuse acute medication, and were refractory, which was defined as failing to have any benefit from at least two classes of preventive medication.\textsuperscript{14} Out of a total of 110 patients enrolled, 29 patients receiving adjustable stimulation and 16 patients receiving preset stimulation completed a 3-month experimental phase after implantation. Another group of 17 patients completed a program of medical management. While the number of headache days, overall pain intensity, and percentage change in the number of headache days did not differ significantly between the groups, the response rate was significantly higher in the adjustable stimulation group (39%) compared to the preset stimulation group (6%) and the medically managed group (0%). Response was defined as at least a 50% reduction of headache days per month or at least a 3-point drop of overall pain intensity on a scale from 0 to 10. An ancillary group consisting of patients who did not initially respond to an occipital nerve block subsequently received the same treatment as the adjustable stimulation group (n = 5 after 3 months), with similar results. The most frequent adverse events were lead migration (24%) and infection at the implantation site (14%).

**Cluster Headache**

Based on positive results from a pilot study with 8 subjects,\textsuperscript{15} a Belgian group recently reported the results of their prospective long-term follow-up of 37 months in 14 patients with unilateral ONS.\textsuperscript{16} Eleven patients (78%) had at least a 90% reduction in attacks, and 9 patients (60%) experienced prolonged freedom of pain for months to years. A side-shift was noted in 5 patients (36%), and isolated autonomic symptoms occurred in 5 patients (36%). Battery depletion was reported in 9 patients (64%), and infection of the implanted material in 3 patients (20%).

Another large study in the United Kingdom retrospectively examined the efficacy of bilateral ONS over a mean follow-up of 18 months with at least a 50% reduction of attacks in 5 out of 14 patients (36%). The most frequent adverse events were that 6 patients (43%) required battery replacement and 4 patients (29%) needed lead or electrode revision.\textsuperscript{17,18}

A multicenter prospective French study with bilateral stimulation reported efficacy (at least 50% reduction of attack frequency) in 10 of 13 patients during a mean follow-up of 15 months. Similar efficacy rates are reported from a German group of 10 patients with an 18-month follow-up period,\textsuperscript{19} and from additional smaller case series amounting to more than 60 patients in total who have been treated with ONS for chronic cluster headache, with more than 50% of the patients responding.

Adverse events requiring surgical revisions occurred in a substantial number of patients, including problems such as lead migration or breakage, infection, battery depletion, muscle contractions, irritation from faulty lead insulation, and local pain over the stimulator. However, the most frequent side effects were paresthesias in the stimulated nerve, which are predictive of good therapeutic response.

**Other Trigeminal Autonomic Headaches**

In hemicrania continua, Burns and coworkers found patient-reported response rates of at least 80% in four out of six patients after a median follow-up of 14 months.\textsuperscript{17} In a case series of five patients receiving ONS for short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and one patient with short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), four patients reported an improvement of at least 50%.

**Other Headaches**

One out of two patients with new daily persistent headache (NDPH) and all eight patients with cervical pain meeting the ICHD-II 13.12 criteria (constant pain caused by compression, irritation, or distortion of cranial nerves or upper cervical roots by structural lesions) had a good response (50% improvement of pain) during ONS.

**Critical Appraisal of Occipital Nerve Stimulation in Primary Headaches**

Despite its increasing use as the neuromodulatory approach of first choice in most primary headaches, ONS therapy has some key issues that remain problematic. Paresthesia as a putative precondition for successful stimulation challenges the design of future studies in terms of true blinding. It is uncertain whether permanent implantation should be based on the response to an externalized test stimulation for 5 to 28 days because clinical effects may not become apparent until several weeks of continuous stimulation. Surgical and device-related complications are unacceptably high in devices with internal pulse generators and connecting subcutaneous leads. Thus, surgical techniques need improvement, and miniaturized and more robust devices are needed. Rechargeable microstimulators have been effective in a number of studies, and the first commercially available devices have been approved for clinical use, and so it will be intriguing to see whether complication rates are lower with these novel devices.
Stimulation of Other Craniofacial Nerves

Other craniofacial nerves have been targeted percutaneously, such as the supraorbital nerve for the treatment of cluster headache and the auriculotemporal nerve in chronic migraine. However, evidence is mainly anecdotal. Preliminary results of a Belgian study on transcutaneous supraorbital nerve stimulation in frequent migraine \( n = 67 \) are promising: 3 months of 20 minutes of stimulation once a day resulted in a significant reduction of headache days per month after 3 months compared to sham stimulation \((-2.06 \text{ days versus } -0.32 \text{ days})\).20

The combined stimulation of the occipital and the supraorbital nerve led to pain reduction of at least 50% in all seven patients with chronic migraine.21 A larger retrospective case series on 44 patients with chronic migraine by the same author, showing a reduction of headache frequency of 81% (a reduction from 19 to 3.6 headaches per month), has been presented in preliminary form. In occipital neuralgia, two out of three patients reported a pain reduction of at least 50% during stimulation of the supra- or infraorbital nerve in combination with the occipital nerve.22

Sphenopalatine Ganglion Stimulation

On the basis of the clinical observation of parasympathetic activation during cluster headache attacks, which is supported by animal experiments, blocks and lesions of the sphenopalatine ganglion (SPG) have been performed for more than 30 years. It is noteworthy that such activation is only observed ictally, resulting in initial reports of acute SPG stimulation from Ansarinia and colleagues, who noted that SPG stimulation but not sham stimulation aborted 61% of attacks within a few minutes in five subjects.23 Likewise, the same group showed that SPG stimulation aborted or substantially ameliorated 50% of beginning migraine attacks in 10 patients.24

These promising results are supported by a multicenter, randomized, double-blind, sham-controlled study on the efficacy of acute stimulation of the SPG in 27 patients with refractory chronic cluster headache. The final study results await publication and have been presented at the 3rd European Headache and Migraine Trust International Congress in London in 2012, reporting clinically relevant pain relief in 67% of headache attacks treated with full stimulation compared to relief in only 8% of attacks treated with sham or sub-perception threshold stimulation. Seven patients (26%) out of 27 achieved acute pain relief, 10 (37%) had a 50% reduction of attack frequency, and 2 (7%) had both.25 Hypoesthesia of the second trigeminal branch, which was transient in 62% of the affected patients, was the most relevant side effect in 47% of the study population.

Vagal Nerve Stimulation

Data on the efficacy of vagal nerve stimulation in primary headaches have been reported anecdotally in single cases and in small case series including chronic daily headache, chronic cluster headache, chronic tension-type headache, and migraine, including some patients with comorbid epilepsy (for review, see Jenkins and Tepper\textsuperscript{26}). Despite good tolerability, with vocal cord paresis, cough, dyspnea, and hoarseness as relevant side effects, electrode and lead revisions are difficult or even impossible because of scar tissue causing permanent adherence of the electrode to the nerve. In the absence of larger studies, this method should be considered primarily in patients with comorbid epilepsy at present. The role of the currently emerging transcutaneous intermittent vagal nerve stimulation on various primary headache syndromes has yet to be determined by controlled studies that are currently being conducted.

Central Approaches

Deep Brain Stimulation

Prophylactic DBS of the posterior hypothalamus has been used in trigeminal autonomic cephalalgias since 2001 on the basis of structural and functional neuroimaging studies and hormonal data suggesting a key role of the target structure.27 Acute stimulation provided no benefit. Several single cases, case series, and one randomized controlled trial have been published, with a total of more than 65 patients with mainly trigeminal autonomic cephalalgias. The prophylactic efficacy of DBS of this brain region has been examined most extensively in chronic cluster headache in more than 50 patients.

Cluster Headache

In chronic cluster headache, a randomized sham-controlled, double-blind, cross-over study with 11 patients yielded ambiguous results. While there was no significant difference in weekly attack frequency between 4 weeks each of active and sham stimulation, 6 of the 11 patients experienced a reduction in attack frequency of at least 50% in the following 10 weeks in the open phase.28 The missing effect in the double-blind period can hardly be interpreted as failure of DBS, because predefined stimulation parameters were used in a rather short experimental period of 4 weeks with short washout periods of 1 week in between. This delayed effect is in line with clinical practice, where optimization of stimulation parameters can be tedious and delayed effects are often seen weeks to months after the beginning of treatment. Results in the open period were comparable to results reported in open studies.

Further case series report that at least 50% of patients had an adequate response to treatment (a 50% or more reduction in attack frequency).29–33 Published follow-up periods of more than 4 years show good long-term efficacy. However, loss of efficacy has been reported in some patients, and it is a matter of dispute whether this problem is attributable to the natural course of the underlying condition or to the development of tolerance to stimulation. Side effects are mostly within the range of those associated with other
DBS targets, mainly explantation of electrodes due to infection. Additionally, syncopes, changes in appetite and thirst, diplopia (mainly with increasing amplitudes), and vertigo occurred in some patients. No relevant effects on clinical autonomic testing were found apart from an increased sympathetic-excitatory tone in the “head-up tilt test.” The circadian rhythm is not impaired by hypothalamic DBS. However, some severe side effects occurred: one patient died from a lethal intracerebral hemorrhage, and another had a panic attack with autonomic disturbances and could not be implanted. Another patient experienced a transient hemiparesis that was classified as a transient ischemic attack. As a consequence, hypothalamic DBS should be restricted to centers with sufficient expertise in stereotactic neurosurgery.

**Use in Other Pain Syndromes**

Hypothalamic DBS has been used with success in other trigeminal autonomic cephalalgias besides cluster headache, such as in three patients with SUNCT syndrome and one patient with chronic paroxysmal hemicrania. While this intervention was not effective in three patients with persistent idiopathic facial pain, all five patients with symptomatic trigeminal neuralgia due to multiple sclerosis reported at least 50% improvement. It seems noteworthy that effects were confined to the first trigeminal branch, so that other regions such as the ventral posterior medial nucleus and the periaqueductal/periventricular gray should be considered, because they have been targeted with success in various forms of facial pain.34,35

This type of stimulation does not induce sensory alterations, and therefore blinding is feasible. Interruption of DBS with the patient blinded to it has repeatedly led to quick aggravation of the underlying headache, although blinding was not routinely implemented in the case series.29,32

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**Table IV**

Efficacy of different neuromodulatory approaches on various primary headaches

<table>
<thead>
<tr>
<th>Approach</th>
<th>CCH</th>
<th>Other TACs</th>
<th>MIG</th>
<th>ON</th>
<th>cTTH</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital nerve stimulation</td>
<td>++</td>
<td>+</td>
<td>+ (CM)</td>
<td>+</td>
<td>?</td>
<td>(+) (ICHD-II 13.12, NDPH)</td>
</tr>
<tr>
<td>Hypothalamic deep brain stimulation</td>
<td>++</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>(-) (PIFP), (+) (sTN)</td>
</tr>
<tr>
<td>Sphenopalatine ganglion stimulation</td>
<td>+</td>
<td>?</td>
<td>(+) EM</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>High cervical spinal cord stimulation</td>
<td>(+)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Vagal nerve stimulation</td>
<td>(+)</td>
<td>?</td>
<td>(+) (CM + EM)</td>
<td>?</td>
<td>(+)</td>
<td>(+) (CDH)</td>
</tr>
</tbody>
</table>

*Abbreviations and symbols:* ++ sound evidence; + moderate evidence; (+) only anecdotal reports or ambiguous results; ?: no studies found; -, lack of efficacy; CCH, chronic cluster headache; CDH, chronic daily headache; CM, chronic migraine; cTTH, chronic tension-type headache; EM, episodic migraine; ICHD-II 13.12, constant pain caused by compression, irritation, or distortion of cranial nerves or upper cervical roots by structural lesions; MIG, migraine; NDPH, new daily persistent headache; PIFP, persistent idiopathic facial pain; ON, occipital neuralgia; sTN, symptomatic trigeminal neuralgia affecting the ophthalmic division; TAC, trigemino-autonomic cephalalgia.

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**High Cervical Spinal Cord Stimulation**

Based on trigemino-cervical convergence in the lower brainstem, Wolter and colleagues established direct stimulation of the high cervical dorsal column in seven patients with chronic cluster headache.36 Continuous stimulation with frequencies between 40 and 110 Hz resulted in pain reduction of at least 50% in six out of seven patients (86%) postoperatively. However, during the follow-up period of up to 78 months, up to four revisions per person were necessary in five out of seven patients owing to lead breakage, dislocation, and battery depletion. As observed in unilateral ONS and DBS, the attacks switched sides in two patients, requiring contralateral electrode placement. These technical shortcomings when electrodes are placed into a highly mobile area of the cervical spine mean that this technique cannot be recommended at present.

**Summary and Recommendations for Clinical Practice**

After an initial focus on hypothalamic DBS, the less invasive technique of ONS is now widely considered the neuromodulatory approach of first choice in many primary headache disorders. Despite their increasing popularity, most approaches lack methodologically sound randomized multicenter studies using an appropriate sham paradigm (Table IV). Especially in ONS, blinding remains an unresolved issue because effective stimulation induces paresthesias, unlike in hypothalamic DBS. SPG stimulation represents an emerging alternative in the acute and possibly prophylactic treatment of chronic cluster headache. The efficacy of various devices for transcutaneous peripheral nerve stimulation (such as the vagal and supraorbital nerves) and their role relative to implantable devices will have to be evaluated in future studies.
From a methodological point of view, future studies should focus on clearly defined endpoints based on objective data (such as the number of headache days per month) rather than on global estimations by patients.

In clinical practice, the selection of suitable patients, the individual allocation of the most appropriate neuromodulatory approach, and further medical care after implantation, often requiring tedious optimization of stimulation paradigms over a lengthy period, are at least as challenging as the implantation procedure itself. Therefore, an interdisciplinary approach involving a team with expertise in both the diagnosis and treatment of headaches and the implantation of invasive neuromodulatory devices is crucial for the success of this promising addition to our armamentarium against intractable primary headaches.

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6. Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, Jürgens TP, et al. Expertise in both the diagnosis and treatment of headaches and further medical care after implantation, often requiring te-

7. 6.  Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, Jürgens TP, et al. Expertise in both the diagnosis and treatment of headaches and further medical care after implantation, often requiring te-

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Tim Jürgens, MD
Department of Systems Neuroscience and Headache Clinic, Department of Neurology
University Medical Center Hamburg-Eppendorf
D-20246 Hamburg, Germany
Email: t.juergens@uke.de
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