Neurol Sci (2017) 38 (Suppl 1):S145–S156
DOI 10.1007/s10072-017-2910-0

New treatments for headache

Kasra Maasumi[1] · Stewart J. Tepper[2] · Alan M. Rapoport[3]

Abstract Headache disorders are common worldwide and often disabling. Until recently, treatments were borrowed from other branches of neurology and medicine. Monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) ligand and receptor, small molecule CGRP receptor antagonist gepants, serotonin$_{1F}$ agonists, new devices to deliver currently available drugs, and neuromodulation devices have recently been in the forefront of headache treatments that are rather specific for various headache disorders. These novel therapies are changing the field of headache medicine. Herein, we update the latest data available for these therapies.

Keywords Calcitonin gene-related peptide (CGRP) · Monoclonal antibodies · Headache treatment · Neuromodulation · Neurostimulation · Magnetic stimulation

Introduction: epidemiology of primary headache disorders

Headache disorders are among the most common and debilitating conditions with which physicians deal. Prevalence data show that tension-type headache is the second most prevalent disorder worldwide [1, 2]. After dental caries, tension-type headache was among the eight diseases affecting more than 10% of the world population in 2013. Tension-type headache affects 1.6 billion people worldwide. Among all neurological conditions, migraine, tension-type headache, and medication overuse headache were among the most prevalent. The 1-year prevalence rate for migraine is 10%, ranging from 4.5 to 6% in men and 14.5–18% in women [3, 4]. The prevalence distribution for migraine has an inverted U shape, i.e., low prevalence in young and old people. The highest prevalence (23.5%) is among females between the ages of 18 and 44 [5–7].

There are various oral medications for the acute and preventive treatment of primary headache disorders. Patients, however, generally do not remain on their medications for long. Hepp et al. reviewed over 8000 patients and reported that adherence to the initial oral migraine preventive medication prescribed was only 25% at 6 months and 14% at 12 months [8]. They further concluded that switching between oral medications is common, but adherence worsens as the patients' cycle through various treatments. It is also known that most patients do not stay on the first triptan prescribed, nor get total relief from these medications [9, 10].

In this review, we will detail some of the latest treatment options in the pipeline for the primary headache disorders. We will focus on the monoclonal antibodies, non-triptan serotonin receptor agonists, and devices that use triptans and ergots with novel delivery systems. Finally, we will discuss the use of neuromodulation.

✉ Kasra Maasumi
Kmaasumi@gmail.com

[1] Neurology, Headache, University of California San Francisco (UCSF), 2330 Post Street Unit 610, San Francisco, CA 94115, USA

[2] The Giesel School of Medicine at Dartmouth, Hanover, NH, USA

[3] University of California Los Angeles, Los Angeles, CA, USA

New oral and injectable treatment options

Some of the most exciting advances in headache prevention are attributed to modulating the effect of CGRP. The development of small molecule CGRP receptor antagonist gepants and monoclonal antibodies that target either the CGRP ligand or its receptor has proceeded for more than 10 years. Early treatments by the small molecule CGRP receptor antagonist gepants either showed signs of liver toxicity or were not commercialized. Today, other gepants are being tested both for acute care and prevention of migraine. There are several pharmaceutical companies working on their development.

Why target CGRP?

CGRP is a 37 amino acid neuropeptide that is a potent vasodilator present ubiquitously in the body. Lars Edvinsson of Lund University, Sweden, performed the early studies on CGRP and then the effect of blocking CGRP on arteries [11]. CGRP mediates neurogenic inflammation and modulates nociceptive input [12]. It is found in trigeminal sensory afferents, other sensory neurons, and the spinal trigeminal nucleus [13]. In 1990s, Goadsby, Edvinsson, and others reported elevated levels of CGRP in the jugular outflow during migraine attacks [14, 15]. It was also found abundantly in the saliva during migraine attacks [15]. Furthermore, levels of CGRP were attenuated by administration of triptans, associated with pain relief [16]. It has also been shown that intravenous injection of CGRP can cause a headache [16]. Interestingly, migraine-like headache occurred only in patients with a history of migraine, while non-migraineurs had a sensation of fullness in the head [17].

Small molecule CGRP receptor antagonists, the gepants

There have been numerous small molecule CGRP receptor antagonists, called gepants, studied so far for the acute treatment of migraine. All were found effective with positive primary outcomes in phase 2 and 3 trials. The earlier animal studies did not show that they constrict blood vessels. There was no sign of liver toxicity in these early trials. When a preventive trial was done with the daily use of one of these antagonists, telcagepant, which had already shown acute care efficacy in two-phase 3 trials, liver toxicity was noted. A follow-up trial requested by the US Food and Drug Administration (FDA), done in patients with menstrually associated migraine, also showed liver toxicity and further work on telcagepant was halted [18–22].

Early studies of gepants

The first gepant described in clinical trials was olcegepant [22, 23]. The trial was a multi-center, double-blind, randomized trial for the acute relief of a migraine attack; it revealed that at 2 h, the 2.5 mg intravenous dose of olcegepant provided 66% of the patients with pain relief compared to 27% for the placebo ($p = 0.001$). The adverse event rate was 25% compared to the placebo, which was 12.5%. The most common side effect was paresthesia; there were no CNS or triptan-like side effects. It was concluded that it was effective in treating migraine acutely. It has not yet been commercialized.

Telcagepant (MK0974), at 300 mg, achieved pain relief at 2 h of 68%, at 400 mg 48.2%, and at 600 mg 67.5% versus rizatriptan 10 mg 69.5% and placebo 46.3% ($p = 0.015$) [24]. In a randomized, parallel-group, placebo-controlled, double-blind, international trial of 1380 patients, telcagepant 300 mg was as effective at treating migraine acutely as zolmitriptan 5 mg but with fewer adverse events [25, 26]. Cui et al. performed a meta-analysis on the efficacy of telcagepant versus placebo and triptans (zolmitriptan or rizatriptan) in 2015. Eight trials were included in the analysis. Pain freedom at 2 h favored telcagepant over placebo (odds ratio = 2.70, 95% confidence interval = 2.27–3.21, $p < 0.001$) There was non-inferiority for telcagepant versus triptans (odds ratio = 0.68, 95% confidence interval = 0.56–0.83, $p < 0.001$). Pain relief at 2 h was better for telcagepant compared to placebo (odds ratio = 2.48, 95% confidence interval = 2.18–2.81, $p < 0.001$; this was not the case when telcagepant was compared with triptans (odds ratio = 0.76, 95% confidence interval = 0.57–1.01, $p = 0.061$) [27]. The development of telcagepant was halted due to an increase in aminotransferases in two patients. A randomized, double-blind, placebo-controlled, multi-center trial by Ho et al. showed that although telcagepant taken daily reduced headache by 1.4 days per month compared to placebo, but there was a 2.5% risk of increased alanine aminotransferase (ALT) [18].

Current studies of gepants

BMS-92771 is an oral gepant in which the phase 2 trial was completed; however, the company that developed it is offering to sell it [21]. It is superior to placebo and is well tolerated. In the double-blind, randomized, placebo-controlled, dose-ranging trial, the authors showed that at 2 h, pain freedom for the 75 mg dose was 31.4% ($p = 0.002$), for the 150 mg dose was 32.9% ($p < 0.001$), and for the 300 mg dose was 29.7% ($p = 0.002$) compared to placebo,

which was 15.3%. A secondary endpoint, sustained pain freedom from 2 to 24 h post dose, demonstrated statistically significant results compared to placebo.

Another oral gepant for which phase 2 dose-ranging data were published is BI 44370 TA. The study was done on 341 subjects with migraine who were treated with 50, 200, and 400 mg of study drug, eletriptan 40 mg or placebo [28]. The primary endpoint was 2 h pain freedom. For the 400 mg dose, the results were 27.4% compared to eletriptan, which was 34.8% and placebo, which was 8.6% ($p = 0.0016$). There are apparently no current plans to proceed with this gepant into phase 3.

Voss et al. performed a phase IIb randomized, double-blind, placebo-controlled trial of oral ubrogepant for the acute treatment of migraine attacks in 2016 [29]. The dose range finding study of 1, 10, 25, 50, and 100 mg compared to placebo was performed for efficacy and tolerability. There were 527 subjects who received the drug and 113 that received placebo. Ubrogepant 100 mg showed superiority over placebo for 2-h pain freedom, 25.5% compared to 8.9%, $p < 0.001$) but no superiority for pain relief at any time point. The failure to show benefit for pain relief was either due to a relatively high placebo response rate, a somewhat low number of patients in the 100 mg dose, or the dose selected, which may have been too low in this dose-ranging study.

Atogepant, antoher oral gepant, is currently being studied in the phase 2 trials as a preventive treatment of episodic migraine (Clinicaltrials.gov NCT02848326).

The development of monoclonal antibodies to CGRP or its receptor

Monoclonal antibodies to CGRP and its receptor have been developed for migraine prevention. They are highly specific for their target. They are not metabolized in the liver and therefore devoid of liver toxicity. They have very long half-lives compared to currently available oral migraine preventive medications. Because of their large molecular size, they cannot cross the blood brain barrier and must be injected intramuscularly, subcutaneously, or infused intravenously [30]. Currently there are four monoclonal antibodies to CGRP or its receptor that are being developed. At the time of this writing (March 2017), they all have completed phase 2 trials and are currently in phase 3 studies: erenumab (Amgen 334) [31, 32] eptinezumab (ALD 403) [33], galcanezumab (LY2951742) [34], and fremanezumab (TEV48125) [35]. These will be described individually in detail.

Erenumab (AMG 334)

The trials for Erenumab (AMG 334) are for episodic and chronic migraine; this is the only antibody of the four that targets the CGRP receptor, not the ligand. Erenumab is a fully human CGRP immunoglobulin G2 (IgG) antibody that binds selectively to the CGRP receptor. It is the only one of the four migraine preventive monoclonal antibodies that is fully human; the other three are humanized. The target is a G protein coupled receptor composed of calcitonin receptor-like receptor and receptor activity modifying protein 1 subunits (RAMP1). At 70 mg, the half-life of erenumab is 21 days, allowing for monthly subcutaneous injections [31, 32]. In a multi-center, randomized, double-blind, placebo-controlled phase 2 trial, the safety and efficacy of erenumab were assessed for prevention of migraine attacks [31]. There were 483 patients enrolled at 59 centers between the ages 18–60 with 4–14 migraine days per month. The primary endpoint was the change in monthly migraine days from baseline for 12 weeks. The mean change in monthly migraine days was 3.4 days fewer at 12 weeks with erenumab at 70 mg compared to 2.3 days fewer with placebo ($p = 0.021$). Adverse events occurred in 54% who received placebo, and 54% of those who received erenumab 70 mg.

There is also a phase 3 randomized, double-blind, placebo-controlled trial for the evaluation of the efficacy and safety of erenumab in migraine prevention (Clinicaltrial.gov NCT02483585). The primary outcome measure is change from baseline in mean monthly migraine days at 3 months. This is for episodic migraine patients with or without aura who have headaches more than 12 months. The erenumab at dose of 70 mg subcutaneously once a month or placebo was administered for the first 12 weeks then followed by open-label phase for 28 weeks.

Phase 2/3 data on Erenumab were presented at the European Headache Federation/Migraine Trust meeting in September 2016 in Glasgow, Scotland. Erenumab 70 and 140 mg were both superior to placebo at reducing migraine days at 12 weeks, showing a 6.6 decrease in migraine days versus a 4.2 decrease in migraine days for placebo, $p < 0.001$. About 40% of patients treated with active drug had at least a 50% decrease in migraine days compared with 24% for placebo. Tolerability was good and comparable to placebo.

Currently, we are awaiting other results of trials pertaining to erenumab. There is an open-label extension study to assess the long-term safety and efficacy of erenumab (Clinicaltrial.gov NCT02174861). There is a randomized, double-blind, placebo-controlled, study on the effect of AMG 334 on exercise time during a treadmill test in patients with stable angina (Clinicaltrial.gov NCT02575833). There is a phase 1 randomized controlled trial (RCT) on the effect of a single dose erenumab on blood pressure given concomitantly with subcutaneous sumatriptan in healthy subjects (Clincialtrial.gov NCT02741310). There is a phase 1 RCT to evaluate the

blockade of CGRP receptor using a single dose of erenumab in preventing PCAP-38-induced migraine, such as attacks (Clinicaltrial.gov NCT 02542605). Another phase 1 RCT evaluates the efficacy, safety, tolerability and pharmacokinetics of erenumab in women with hot flashes associated with menopause (Clinicaltrial.gov NCT 01890109).

Eptinezumab (ALD 403)

The eptinezumab trials are for episodic and chronic migraine attacks, and the only ones looking at an intravenous dose. The current data available for this drug are from a phase 2 trial. Eptinezumab is a humanized CGRP IgG1 antibody that binds to both alpha and beta forms of the human CGRP [33]. It has a half-life of 31 days at 1000 mg dose, given intravenously.

In a randomized, double-blind, placebo-controlled exploratory proof of concept phase 2 trial, Dodick et al. assessed the safety, tolerability, and efficacy of eptinezumab in patients with 5–14 migraine days per 28-day period who were between the ages 18–55. The trial enrolled 163 patients, 81 of whom received 1000 mg of eptinezumab, while 82 received placebo only once in 3 months. After 5–8 weeks, the mean change in migraine days compared to baseline was 5.6 days fewer for the eptinezumab group and 4.6 days fewer for the placebo group ($p = 0.0306$). There were no safety concerns noted. A post hoc analysis showed that 16% of the subjects had a 100% responder rate for pain relief, 24% had a 75% responder rate, and 28% had a 50% responder rate during the 12 weeks of the trial.

The current trial in progress is entitled "A Parallel Group, Double-Blind, Randomized, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of ALD 403 Administered Intravenously in Patients With Chronic Migraine" (Clinicaltrials.gov NCT02974153). Results may be available in 2017. An open-label trial is also under way titled "An Open Label Trial to Evaluate the Safety of ALD403 Administered Intravenously in Patients With Chronic Migraine" (Clinicaltrials.gov NCT02985398).

Galcanezumab (LY2951742)

The clinical trials for galcanezumab are for episodic and chronic migraine as well as cluster headaches. The treatment is given as a single subcutaneous injection twice a month. Galcanezumab is a humanized monoclonal antibody selectively binding to CGRP ligand with a half-life of 28 days [34]. In a phase 2 RCT, the efficacy and safety of galcanezumab were assessed at 35 centers in patients between the ages of 18–65 with 4–14 migraine days per month. The dose was 150 mg galcanezumab in comparison with placebo. The primary endpoint was the mean change in number of migraine headache days per 28-day period between baseline and 12 weeks. Safety was assessed over 24 weeks. Of the 218 patients, 108 of them received galcanezumab, and the rest received placebo. The mean change in headache days after 12 weeks compared to baseline was 4.2 fewer days for those receiving the drug and 3 days fewer for those receiving placebo ($p = 0.0030$). Adverse events occurred in a small percentage of the patients.

RCTs in phase 3 evaluating galcanezumab for episodic and chronic cluster headaches are underway (Clinicaltrial.gov NCT02438826 and NCT02397473).

Fremanezumab (TEV48125)

The trials for fremanezumab are for episodic and chronic migraine and also for cluster headache. It was the first of the monoclonals to be reported in a phase 2 trial for chronic migraine. It is given as a monthly subcutaneous injection and targets the CGRP ligand. In a phase 2b multi-center, randomized, double-blind, placebo-controlled trial on episodic migraineurs, the efficacy and safety of fremanezumab were assessed in patients between the ages of 18 and 65 with 8–14 headache days per month, which is high-frequency episodic migraine [35]. The primary endpoints for episodic migraine were change in migraine days from baseline to 12 weeks as well as safety and tolerability. There were 297 patients evaluated, 95 of them received the 225 mg dose and 96 received the 675 mg dose. The change in number of migraine days after 12 weeks was 6.09 days fewer in the 675 mg dose group, 6.27 days fewer in the 225 mg dose group, and 3.46 fewer days in the placebo group ($p < 0.0001$). Adverse events occurred in 59% in the group who received 675 mg dose, 46% in the 225 mg dose group, and 56% of the placebo group.

Fremanezumab was also evaluated at the same time for chronic migraine [36]. This was a multi-center, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, phase 2b trial. The participants were patients between the age of 18 and 65 with chronic migraine who received three 28-day treatment cycles of subcutaneous fremanezumab at doses of 675 mg in the first treatment cycle, 225 mg in the second and third treatment cycles each. This dosage was compared to 900 mg in all three treatment cycles as well as placebo. The primary endpoints were change from baseline in total headache hours during weeks of 9–12, which are the third treatment cycle, along with safety and tolerability. Overall, there were 264 participants. The mean change from baseline in terms of the number of headache hours during the third treatment cycle was 67.51 h fewer in the 900 mg group, 59.84 h fewer in the groups that received 675/225 mg injections, and finally 37.10 h fewer in the placebo group.

Adverse events were 47% in the 900 mg group, 53% in the 675/225 mg group, and 40% in the placebo group.

There are also ongoing phase 3 studies of fremanezumab on episodic and chronic cluster headaches (Clinicaltrial.gov NCT02945046 and NCT02964338).

Lasmiditan: a Serotonin$_{1F}$ receptor agonist

The 5-HT$_{1F}$ receptor agonists are alternatives to the triptans, which are mostly agonists at the 5-HT$_{1B/1D}$ receptors. The unique features of pure 5-HT$_{1F}$ receptor agonists are that they are anti-inflammatory, centrally active, and do not constrict vessels. Some triptans have minor 1F activity but are also vasoconstrictors as they have 1B activity.

Ferrari et al. evaluated lasmiditan in a randomized, multi-center, placebo- controlled, double-blind proof of concept trial in 130 patients using IV lasmiditan versus placebo [37]. The primary outcome was headache response, defined as improvement from moderate or severe headache at baseline to mild or no headache at 2 h post infusion. Of those that received lasmiditan, 54–75% showed 2 h headache response compared to 45% for the placebo ($p = 0.0126$). They concluded that at 20 mg IV and higher, lasmiditan proved effective in the acute treatment of migraine. Studies were then planned for an oral form of the drug.

In a phase 2 trial, the efficacy and safety of oral lasmiditan for acute treatment of migraine were assessed [38]. Doses of 50, 100, 200, or 400 mg of lasmiditan or placebo were tested on 512 patients with assessment of 2-h pain relief. The percentage of patients improving on 50 mg dose compared to placebo showed a difference of 17.9% ($p = 0.022$), for 100 mg, the difference was 38.2% ($p < 0.0001$), for 200 mg, the difference was 28.8% ($p < 0.0018$), and for 400 mg, the difference was 38.7% ($p < 0.0001$). The most common side effects were dizziness and paresthesia along with fatigue and nausea, and the rates were fairly high. The authors concluded that the oral lasmiditan is safe and effective in treatment of acute migraine, but tolerability was an issue.

In the phase 3 trial of oral lasmiditan, the primary outcome measure was the proportion of subjects being pain free at 2 h post dose; it was 32.2% for 200 mg versus 15.3% for placebo ($p < 0.001$). The doses tested were 50, 100 and 200 mg. A key secondary endpoint was freedom of the most bothersome symptom. At 100 mg, the results were 40.9%, at 200 mg 40.7%, and placebo was 29%. ($p < 0.001$). Tolerability was better in the phase 3 than in the phase 2 trial, but there remain questions on the methodology used in phase 3 and the technique used for collection of adverse event data (Clinicaltrials.gov NCT02605174).

New devices for currently approved medications

Sumatriptan 3 mg subcutaneous injection (Zembrace SYMTOUCH)

This device made by Promius Pharma LLC, the American arm of Dr. Reddy's Laboratory Ltd, India, provides a disposable auto-injector prefilled with 3 mg of sumatriptan. In a recent trial, Cady et al. attempted to justify the use of the 3 mg dose subcutaneous sumatriptan as opposed to the 6 mg dose in a randomized, double-blind, cross-over study [39]. They compared the efficacy and tolerability of the 3 mg SC sumatriptan (DFN-11) with the 6 mg SC sumatriptan in 20 adults who had rapidly escalating migraine attacks. None of the results was statistically significant. They reported that at 1 h post injection, 50% of patients experienced pain relief with the 3 mg dose and 52.6% with the 6 mg dose. Similar types and numbers of adverse events were found for both doses including paresthesia, neck pain, flushing, and involuntary muscle contractions of the neck.

Another phase 2 trial is also in progress titled "Pilot Study of DFN-11 Injection in Medication Overuse Headache" (Clinicaltrials.gov NCT02583425). The advantage of using the 3-mg dose injection may be mainly for those who cannot tolerate the higher doses of 4 and 6 mg. It may also be helpful to lower the total daily or weekly dose of sumatriptan in cluster patients and those with frequent migraine attacks, although it was not studied for these indications.

Sumatriptan breath-powered intranasal powder (Onzetra Xsail)

This device from Avanir pharmaceuticals, Inc. is a nasal powder formulation of sumatriptan that is blown into each nostril, for acute treatment of migraine in adults. The amount of sumatriptan used is 11 mg in each nostril, although slightly less is actually delivered. When the device was under development, it was called AVP-825 or Optinose.

Obaidi et al. assessed the pharmacokinetic profile of 22 mg sumatriptan powder given intranasally [40]. In an open-label, cross-over, comparative bioavailability study, they compared it with 20 mg sumatriptan liquid nasal spray, a 100 mg tablet, and a 6 mg subcutaneous injection. They concluded that the breath-powered intranasal delivery is more efficient form of drug delivery providing a higher peak and earlier exposure with a lower dose than the nasal spray and faster absorption that either nasal spray or oral form.

The efficacy and safety of the device were assessed by Cady et al. in a phase 3 study comparing it to an identical

device containing lactose powder (placebo) [41]. This was a double-blind, placebo-controlled, parallel-group study with the primary endpoint of 2-h pain relief. They enrolled 223 patients into the study. There were 68% of the patients on verum who had 2 h pain relief compared to 45% on placebo ($p = 0.002$). At 2 h, 38% of the patients on verum achieved pain freedom compared to 17% on placebo ($p = 0.008$). There were no serious adverse effects (AE) and few triptan AEs.

Tepper et al. compared the efficacy, tolerability and safety of the AVP-825 with 100 mg oral sumatriptan for the acute treatment of migraine in a comparative effectiveness trial across at least five attacks in a double-dummy design [42]. They enrolled total of 275 subjects in the trial. The primary endpoint was the mean value of the summed pain intensity differences through 30-min post dose, comparing the oral with the nasal sumatriptan. The secondary endpoints were pain relief, pain freedom, and pain reduction as well as safety across multiple times. There was a significant reduction in migraine pain intensity in the first 30 min ($p < 0.001$) for the powder, which continued for 2 h. At 2 h, the tablet caught up with the nasal form. However, in the first 2 h, the dry nasal powder was consistently superior to the tablet for efficacy despite the lower dose of the nasal formulation with lower adverse events. The main complaints were nasal discomfort and abnormal taste. This device has been marketed in the US since May 2016. This formulation would be appropriate for patients requiring a non-oral formulation, those with quick onset to peak headaches, and for those with triptan sensations from conventional oral triptan doses.

Dihydroergotamine (DHE) Oral Inhaler (Semprana)

Shrewsbury et al. conducted a randomized, double-blind, placebo-controlled trial of two doses of inhaled DHE on 19 subjects in 2008 [43]. They concluded that it resulted in rapid and efficient systemic absorption. There were no clinically relevant safety issues observed. In another study, Shrewsbury also investigated the pulmonary absorption of DHE and compared its safety, pharmacokinetic, and metabolic profile in various doses using the Tempo Inhaler from MAP Pharmaceuticals Inc, in 18 healthy volunteers [44]. They concluded that its delivery of 1 mg was slightly lower than IV administration.

Tepper et al. also conducted a post hoc sub-analysis using data from the Freedom-301 study, which had enrolled 903 patients in a randomized, double-blind, placebo-controlled phase 3 trial in 2008. It evaluated the efficacy of orally inhaled DHE for the acute treatment of migraine between 1 and 8 h post migraine onset [45]. They concluded that the orally inhaled DHE is effective in treating migraine irrespective of the time of the treatment.

In a review, Tepper further elaborated that DHE has persistent receptor binding that may account for its use in treating allodynia and central sensitization in prolonged migraine and status migrainosus among the many subtypes of migraine [46]. The inhaled formulation has a lower maximal serum concentration than the IV formulation resulting in markedly decreased nausea and vomiting.

In the Freeedom-301 phase 3 study, 903 adults with episodic migraine had superior 2 h results from DHE compared to the placebo for pain relief (58.7 versus 34.5%, $p < 0.0001$), phonophobia free (52.9 versus 33.8%, $p < 0.0001$), photophobia free (46.6 versus 27.2%, $p < 0.0001$), and nausea free (67.1 versus 58.7%, $p = 0.0210$). In addition, more patients were pain free at 2-h post treatment compared to placebo (28.4 versus 10.1%, $p < 0.0001$) [47]. Tolerability was good, and no pulmonary signal was reported.

There have been concerns noted by the FDA with chemistry, manufacturing, and controls (CMC) for the DHE inhaler, but not with efficacy or safety. If these CMC issues are resolved, the brand name of the DHE inhaler is anticipated to be Semprana (formerly Levadex).

Zolmitriptan microneedle patch (ZP)

A randomized, double-blind, multi-center, parallel-group, dose-ranging comparison trial has just been reported by press release from Zosano for the safety and efficacy of the ZP-zolmitriptan intracutaneous microneedle system for the acute treatment of migraine (Clinicaltrial.gov NCT02745392). This small patch, the size of a coin, is placed by an applicator and contains numerous microneedles impregnated with zolmitriptan. The primary endpoint was pain freedom at 2 h using 1, 1.9, and 3.8 mg single patch administration compared to placebo. The results were all statistically significant. There were 77 patients on placebo, 79 on 1 mg, 83 on 1.9 mg, and 82 on 3.8 mg. Pain freedom at 2 h was 14.3% for placebo, 30.4% for the 1 mg dose ($p = 0.0149$), 27.7 for the 1.9 mg dose ($p = 0.0351$), and 41.5% for the 3.8 mg ($p = 0.0001$). The secondary endpoint was freedom from most bothersome symptom at 2 h. The only result that was statistically significant was for the 3.8 mg dose, which was 68.3%, compared to placebo, which was 42.9% ($p = 0.0009$). Tolerability was good.

Neuromodulation

Neuromodulation is a rapidly growing branch of headache medicine therapy, whereby non-invasive or minimally invasive techniques are used to modulate pain by targeting specific areas of the central and peripheral nervous system [48].

Non-invasive neuromodulation

Non-invasive forms of neuromodulation include single pulse transcranial magnetic stimulation (sTMS), transcutaneous supraorbital nerve stimulation (tSNS), non-invasive vagal nerve stimulation (nVNS), and caloric vestibular stimulation (CVS). Both sphenopalatine ganglion stimulation and occipital nerve stimulation are more invasive, and transcranial direct current stimulation (tDCS) has not been studied in the United States for headache disorders.

Single pulse transcranial magnetic stimulation (sTMS)

Single pulse TMS, from eNeura, Inc., is effective and FDA approved for acute treatment for migraine with aura [49]. Both sTMS and repetitive TMS (rTMS) are being studied for migraine prevention [50–56]. The magnet generates an electrical field penetrating the cortex up to 3 cm deep. It is believed that the sTMS works on migraine with aura by inhibiting occipital cortical spreading depression. It is approved in Europe for the acute treatment of migraine with and without aura and for migraine prevention.

To evaluate the responses of patients to sTMS in clinical practice, Bhola et al. surveyed 190 patients with migraine with and without aura over a 3-month treatment period using the device in an open-label study [49]. She found that 62% of the patients reported pain relief, 52% reported less nausea, 55% reported less photophobia, and 53% reported less phonophobia. At 3 months, there was a reduction in headaches days from 12 to 9 among those with episodic migraine and a reduction from 24 to 16 among those with chronic migraine. A larger open-label study, the ESPOUSE study, for prevention of migraine, has been completed in the United States, and preliminary positive data were presented at the European Headache Federation/Migraine Trust meeting in September, 2016 in Glasgow, Scotland.

Transcutaneous supraorbital nerve stimulation (tSNS)

The frontal nerve is a part of the ophthalmic division of the trigeminal nerve and it terminates in the supraorbital and supratrochlear nerves. These two nerves provide sensation to the front and top of the head. By inhibiting the nociceptive transmission via transcutaneous electrical stimulation, it is believed that the nociceptive activity can be modulated more centrally. A device named Cefaly made by Cefaly Technology, Belgium has been approved for migraine prevention in the United States [57, 58].

Schoenen and colleagues published the only RCT on tSNS [59]. In 67 patients with episodic migraine, the 50% responder rate after 3 months was 38.2% compared to the sham group, which was 12.1%. The acute migraine medication intake was reduced by 36.7% in the active group. A study on the acute treatment of migraine is underway.

Non-invasive vagal nerve stimulation (nVNS)

The vagus or 10th cranial nerve has mixed sensory and motor nerve components [48]. It is both an afferent and efferent nerve, which is about 70% sensory. It carries parasympathetic preganglionic fibers and also cutaneous sensory and visceral afferent traffic.

A transcutaneous, non-invasive device has been developed by electro-Core LLC, NJ USA called GammaCore. It stimulates the cervical part of the vagal nerve. It is under consideration by the FDA for the indication of acute treatment of cluster headache. They have also applied for migraine acute care and prevention indications. It is a hand held device that is approved for treatment of migraine and cluster headaches in many countries in the world.

The device clearly stimulates just the afferent vagal fibers, preferentially activating afferent A and large B fibers, not C or efferent pathways that mediate bradycardia and bronchoconstriction in data presented by Nonis and colleagues at the American Academy of Neurology meeting in 2016. nVNS suppresses rat cortical spread depression (CSD) and inhibits central trigeminovascular and thalamocortical pathways without affecting blood pressure or pulse [60].

Several open-label studies on nVNS in acute and preventive treatment of migraine have been published. In one by Barbanti et al., open-label data on treatment of high-frequency episodic migraine and chronic migraine in 48 patients showed at 2 h, the proportion of patients with pain freedom was 39.6%, and the proportion of patients with pain relief was 64.6% [61–64].

In another open-label trial, Grazzi and colleagues studied the nVNS in mini-prevention for menstrually related migraine. They reported, "The number of menstrual migraine/menstrually related migraine days per month was significantly reduced from baseline (mean ± standard error, 7.2 ± 0.7 days) to the end of treatment (mean ± standard error, 4.7 ± 0.5 days; $p < 0.001$) (primary end point). Of all subjects, 39% (95% confidence interval: 26%, 54%) (20/51) had a ≥ 50% reduction (secondary end point). For the other secondary end points, clinically meaningful reductions in analgesic use (mean change ± standard error, −3.3 ± 0.6 times per month; $p < 0.001$), 6-item Headache Impact Test score (mean change ± standard error, −3.1 ± 0.7; $p < 0.001$), and Migraine Disability Assessment score (mean change ± standard error, −11.9 ± 3.4; $p < 0.001$) were observed, along with a modest reduction in pain intensity (mean change ± standard error, −0.5 ± 0.2;

$p = 0.002$). There were no safety/tolerability concerns." [65].

In an RCT for chronic migraine, with two 90s pulses delivered three times daily, the primary endpoint of reduced headache days at 2 months was not significant. However, there appeared to be reduction of headache days per month clinically evident over 6 months of open-label use [66].

There are two published RCTs for the treatment of cluster headache (CH) published at the time of this writing (March 2017). In the first, nVNS + standard of care was compared with standard of care alone for the CH prevention. The PREVA study showed reduced CH attacks per week from baseline, significant for the nVNS group and positive secondary endpoints of the 50% responder rate and reduced use of rescue medications including oxygen compared with standard of care alone [67].

In the first of two planned RCTs for the acute treatment of CH, the nVNS failed to relieve CH attacks in all comers at 15 min, the primary endpoint. There were significant methodologic problems with the study. However, the ACT1 study clearly showed nVNS could relieve episodic CH attacks at 15 min, while was unsuccessful stopping attacks in chronic CH [68].

Caloric vestibular stimulation (CVS)

Caloric vestibular stimulation (CVS) is a new technique for inhibitory central neuromodulation. The contiguity of the vestibular and trigeminal systems at the point of entry and in transit within the brainstem offers the opportunity for cross-talk and down regulation of central pain conditions, such as migraine.

A device which delivers fluctuating thermal changes in the vestibular pathways, tightly controlled to avoid vertigo and nausea but set with inhibitory parameters, has been studied in prevention of episodic migraine, with reports presented at the American Headache Society annual scientific meeting in San Diego and the European Headache Federation/Migraine Trust meetings in Glasgow 2016. Black et al. showed evidence that CVS treatment can elicit changes in cerebral blood flow physiology consistent with the neuromodulation of brainstem centers [69].

The data presented were from a placebo controlled, blinded, home-use protocol trial (Clinicaltrials.gov NCT02866084), which was completed at six sites enrolling patients with 4–14 headache days per month. Primary and secondary endpoints were positive. Per protocol for headache days at 3 months versus baseline results were: active ($n = 28$); placebo ($n = 18$); active: -3.6 headache days vs. baseline ($p < 0.0001$). That is, active versus sham showed a -2.7 headache day decrease ($p = 0.012$). In the Intention To Treat (ITT) analysis, active ($n = 34$); placebo ($n = 18$): active: -3.2 HA days versus baseline ($p < 0.0001$). That is, active versus sham showed a -2.4 headache day decrease ($p = 0.034$). Secondary endpoints reported as positive were 50% responder rates, use of acute medications, mood, cognition, and balance.

Adverse events were essentially the same as sham. Adverse events reported in >1 patient included nausea, dizziness, ear symptoms, and tinnitus. Both placebo and active groups reported dizziness in four patients each.

Minimally invasive neuromodulation

Minimally invasive neuromodulation forms involve sphenopalatine ganglion (SPG) stimulation and occipital nerve stimulation (ONS).

Sphenopalatine ganglion stimulation (SPGs)

The sphenopalatine or pterygopalatine ganglion (SPG) receives preganglionic parasympathetic fibers originating in the superior salivatory nucleus (SSN). These fibers synapse in the SPG and then postganglionic parasympathetic pathways exit and terminate in autonomic and secretory glands of the face. Postganglionic sympathetic fibers traverse the SPG without synapse on their course to similar destinations. Afferent trigeminal pathways also pass through the SPG.

For many years, physicians have tried to block the SPG to treat migraine and especially cluster headache. It has been chemically inactivated, surgically altered or removed, anesthetized with cocaine and with 4% lidocaine. It can be stimulated at low frequency to activate cluster headache and at high frequency to block it.schy [70]. A small SPG stimulator, without wires or batteries, has been designed and is being tested by Autonomic Technologies, Inc., in Silicon Valley, California. The stimulator is implanted over the ganglion via an oral entry done under anesthesia, and it is remotely activated at the start of each cluster attack. In data from a published RCT by Schoenen et al., later expanded to a larger number of patients and presented at international headache meetings, pain relief was achieved by 67% of the 566 acute attacks of cluster headache at 15 min compared to 7% of the placebo and sham patients. In addition, the device showed preventive effects, with 42% of patients manifesting an 89% decreased attack frequency [71–73].

Barloese et al. monitored the self-reported attack frequency, headache disability, and medication intake in 33 patients with refractory chronic cluster headache [74]. It was an open-label follow-up study in which patients were followed for 2 years after the insertion of the SPG stimulator. They reported that 30% of the patients experienced at least one period of complete attack remission.

This wireless, remote controlled stimulator is currently approved in Europe for treatment of chronic cluster headache and has been studied for migraine, with a submission for CE mark at the time of this writing (March 2017). The registration study in the US for chronic cluster headache is underway,

Occipital nerve stimulation (ONS)

As an alternative treatment for prevention of intractable chronic migraine and cluster headache, ONS stimulation has been under investigation. The idea is to stimulate the large sensory afferents to cause pain reduction by inhibiting nociceptive activity in c-fibers and a-delta fibers as well as possible central inhibition. There have been three RCTs for ONS for prevention of chronic migraine, two of which have been published in peer-reviewed papers. Neither of the two studies which had primary endpoints reached the primary endpoint, and the third negative study was exploratory. One of the three, by Lipton and colleagues, was presented at the International Headache Congress in 2012 but never published fully. The other two studies, as noted, were negative [75, 76]. There are open-label reports of effectiveness, and open-label studies that look at the efficacy of ONS combined with supraorbital and supratrochlear nerve stimulation, but it is well to remember the negative RCTs [77, 78].

Adverse events for ONS include electrode migration, intolerance to paresthesias, cable breakage, pain, muscular spasm, infection, and battery depletion. In 2014, the EU rescinded the CE Mark approval for the St Jude Genesis ONS device for headaches because of these issues.

Maximally invasive neuromodulation

Deep brain stimulation (DBS)

The suprachiasmatic nucleus of the posterior hypothalamus is involved in the pathogenesis of cluster headache [79]. In cases of medically refractory cluster headaches, DBS has been investigated as a treatment option [50, 80–84]. Overall, about 60% of the published cases in the literature report at least 50% reduction in their cluster attack frequency [85]. The first group to refer a patient for this operation was headed by Dr. Gennaro Bussone and Massimo Leone at the Istituto Neurologico C Besta in Milan, Italy. The neurosurgeons performing the operation were Drs. Broggi and Franzini. They had excellent results with very few major complications putting the electrode in the hypothalamic/rostral midbrain area. Some patients are getting excellent relief many years later, even with bilateral implants. Other groups had major complications, and enthusiasm for the procedure has waned.

Conclusions

Headaches are some of the most painful and disabling disorders affecting many people worldwide. So far, for migraine prevention, we have been utilizing medications that were initially developed for other disorders, such as antiepileptic drugs, antihypertensive drugs, or antidepressants. However, new medications and devices have been developed that are targeting primary headache disorder treatment, including migraine and cluster headache. These include CGRP monoclonal antibodies, small molecule CGRP receptor antagonist gepants, $5HT_{1F}$ receptor agonists, and neuromodulation. We also have new acute care treatments in the form of medications, stimulators, and devices with better delivery of older drugs. These new medications and tools will not only help many patients in the near future, but will further open the door to new treatment trials so we can hone the results of treatment of primary headache disorders.

Compliance with ethical standards

Conflict of interest Kasra Maasumi: none. Stewart Tepper: Research grants (no personal compensation): Alder, Allergan, Amgen, ATI, Avanir, Dr. Reddy's, Scion Neurostim, Teva, Zosano; Consultant: Acorda, Alder, Allergan, Amgen, ATI, BioVision, Dr. Reddy's, Eli Lilly, Kimberly-Clark, Pernix, Pfizer, Scion Neurostim, Teva, Zosano; Royalties: Springer; Salary: Dartmouth-Hitchcock Medical Center, American Headache Society; Stock Options: ATI. Alan Rapoport: Is on the Speakers Bureau of Avanir and Depomed. He has consulted for Acorda, Amgen, Autonomic Technologies, Avanir, Depomed, Promius, Impax, Lilly, Pernix, Teva and Zosano.

References

1. Global Burden of Disease Study 2013 Collaborators (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386:743–800
2. Leonardi M, Raggi A (2013) Burden of migraine: international perspectives. Neurol Sci 34(Suppl 1):S117–S118
3. Stewart WF, Lipton RB, Celentano DD, Reed ML (1992) Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. JAMA 267:64–69
4. Maasumi K, Tepper SJ, Kriegler JS (2017) Menstrual migraine and treatment options: review. Headache. 57:194–208
5. Burch RC, Loder S, Loder E, Smitherman TA (2015) The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache. 55:21–34
6. Lipton RB, Bigal ME (2005) Migraine: epidemiology, impact, and risk factors for progression. Headache 45(Suppl 1):S3–s13

7. Smitherman TA, Burch R, Sheikh H, Loder E (2013) The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 53:427–436
8. Hepp Z, Dodick DW, Varon SF, Chia J, Matthew N, Gillard P, Hansen RN, Devine EB (2016) Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: a retrospective claims analysis. Cephalalgia. doi:10.1177/0333102416678382
9. Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, Peterson J, Coyle D, Skidmore B, Gomes T, Clifford T, Wells G (2015) Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. Headache. 55(Suppl 4):221–235
10. Cady RK, Maizels M, Reeves DL, Levinson DM, Evans JK (2009) Predictors of adherence to triptans: factors of sustained vs lapsed users. Headache 49:386–394
11. Edvinsson L, Chan KY, Eftekhari S, Nilsson E, de Vries R, Saveland H, Dirven CM, Danser AH, MaassenVanDenBrink A (2010) Effect of the calcitonin gene-related peptide (CGRP) receptor antagonist telcagepant in human cranial arteries. Cephalalgia 30:1233–1240
12. Russo AF (2015) Calcitonin gene-related peptide (CGRP): a new target for migraine. Annu Rev Pharmacol Toxicol 55:533–552
13. Kageneck C, Nixdorf-Bergweiler BE, Messlinger K, Fischer MJ (2014) Release of CGRP from mouse brainstem slices indicates central inhibitory effect of triptans and kynurenate. J Headache Pain 15:7
14. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28:183–187
15. Ho TW, Edvinsson L, Goadsby PJ (2010) CGRP and its receptors provide new insights into migraine pathophysiology. Nat Rev Neurol 6:573–582
16. Asghar MS, Hansen AE, Amin FM, van der Geest RJ, Koning P, Larsson HB, Olesen J, Ashina M (2011) Evidence for a vascular factor in migraine. Ann Neurol 69:635–645
17. Petersen KA, Lassen LH, Birk S, Lesko L, Olesen J (2005) BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation. Clin Pharmacol Ther 77:202–213
18. Ho TW, Connor KM, Zhang Y, Pearlman E, Koppenhaver J, Fan X, Lines C, Edvinsson L, Goadsby PJ, Michelson D (2014) Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology 83:958–966
19. Ho TW, Ho AP, Ge YJ, Assaid C, Gottwald R, MacGregor EA, Mannix LK, van Oosterhout WP, Koppenhaver J, Lines C, Ferrari MD, Michelson D (2016) Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. Cephalalgia 36:148–161
20. Hewitt DJ, Aurora SK, Dodick DW, Goadsby PJ, Ge YJ, Bachman R, Taraborelli D, Fan X, Assaid C, Lines C, Ho TW (2011) Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. Cephalalgia 31:712–722
21. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ (2014) BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia 34:114–125
22. Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM (2004) Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med 350:1104–1110
23. Yao G, Yu T, Han X, Mao X, Li B (2013) Therapeutic effects and safety of olcegepant and telcagepant for migraine: a meta-analysis. Neural Regen Res 8:938–947
24. Ho TW, Mannix LK, Fan X, Assaid C, Furtek C, Jones CJ, Lines CR, Rapoport AM (2008) Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. Neurology 70:1304–1312
25. Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, Leibensperger H, Froman S, Assaid C, Lines C, Koppen H, Winner PK (2008) Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. Lancet 372:2115–2123
26. Connor KM, Shapiro RE, Diener HC, Lucas S, Kost J, Fan X, Fei K, Assaid C, Lines C, Ho TW (2009) Randomized, controlled trial of telcagepant for the acute treatment of migraine. Neurology 73:970–977
27. Cui XP, Ye JX, Lin H, Mu JS, Lin M (2015) Efficacy, safety, and tolerability of telcagepant in the treatment of acute migraine: a meta-analysis. Pain Pract 15:124–131
28. Diener HC, Barbanti P, Dahlof C, Reuter U, Habeck J, Podhorna J (2011) BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. Cephalalgia 31:573–584
29. Voss T, Lipton RB, Dodick DW, Dupre N, Ge JY, Bachman R, Assaid C, Aurora SK, Michelson D (2016) A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. Cephalalgia 36:887–898
30. Wang W, Wang EQ, Balthasar JP (2008) Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 84:548–558
31. Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, Saper J, Cady R, Chon Y, Dietrich J, Lenz R (2016) Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 15:382–390
32. Shi L, Lehto SG, Zhu DX, Sun H, Zhang J, Smith BP, Immke DC, Wild KD, Xu C (2016) Pharmacologic characterization of AMG 334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. J Pharmacol Exp Ther 356:223–231
33. Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J (2014) Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 13:1100–1107
34. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS (2014) Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol 13:885–892
35. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, Loupe PS, Burstein R, Newman LC, Lipton RB (2015) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 14:1081–1090
36. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC, Burstein R, Loupe PS, Ma Y, Yang R, Silberstein SD (2015) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 14:1091–1100
37. Ferrari MD, Farkkila M, Reuter U, Pilgrim A, Davis C, Krauss M, Diener HC (2010) Acute treatment of migraine with the

selective 5-HT1F receptor agonist lasmiditan–a randomised proof-of-concept trial. Cephalalgia 30:1170–1178
38. Farkkila M, Diener HC, Geraud G, Lainez M, Schoenen J, Harner N, Pilgrim A, Reuter U (2012) Efficacy and tolerability of lasmiditan, an oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. Lancet Neurol 11:405–413
39. Cady RK, Munjal S, Cady RJ, Manley HR, Brand-Schieber E (2017) Randomized, double-blind, crossover study comparing DFN-11 injection (3 mg subcutaneous sumatriptan) with 6 mg subcutaneous sumatriptan for the treatment of rapidly-escalating attacks of episodic migraine. J Headache Pain 18:17
40. Obaidi M, Offman E, Messina J, Carothers J, Djupesland PG, Mahmoud RA (2013) Improved pharmacokinetics of sumatriptan with breath powered nasal delivery of sumatriptan powder. Headache 53:1323–1333
41. Cady RK, McAllister PJ, Spierings EL, Messina J, Carothers J, Djupesland PG, Mahmoud RA (2015) A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (The TARGET Study). Headache 55:88–100
42. Tepper SJ, Cady RK, Silberstein S, Messina J, Mahmoud RA, Djupesland PG, Shin P, Siffert J (2015) AVP-825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral sumatriptan in the acute treatment of migraines (The COMPASS study): a comparative randomized clinical trial across multiple attacks. Headache 55:621–635
43. Shrewsbury SB, Kori SH, Miller SD, Pedinoff A, Weinstein S (2008) Randomized, double-blind, placebo-controlled study of the safety, tolerability and pharmacokinetics of MAP0004 (orally-inhaled DHE) in adult asthmatics. Curr Med Res Opin 24:1977–1985
44. Shrewsbury SB, Cook RO, Taylor G, Edwards C, Ramadan NM (2008) Safety and pharmacokinetics of dihydroergotamine mesylate administered via a Novel (Tempo) inhaler. Headache 48:355–367
45. Tepper SJ, Kori SH, Goadsby PJ, Winner PK, Wang MH, Silberstein SD, Cutrer FM (2011) MAP0004, orally inhaled dihydroergotamine for acute treatment of migraine: efficacy of early and late treatments. Mayo Clin Proc 86:948–955
46. Tepper SJ (2013) Orally inhaled dihydroergotamine: a review. Headache 53(Suppl 2):43–53
47. Aurora SK, Silberstein SD, Kori SH, Tepper SJ, Borland SW, Wang M, Dodick DW (2011) MAP0004, orally inhaled DHE: a randomized, controlled study in the acute treatment of migraine. Headache 51:507–517
48. Puledda F, Goadsby PJ (2016) Current approaches to neuromodulation in primary headaches: focus on vagal nerve and sphenopalatine ganglion stimulation. Curr Pain Headache Rep 20:47
49. Bhola R, Kinsella E, Giffin N, Lipscombe S, Ahmed F, Weatherall M, Goadsby PJ (2015) 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 16:535
50. Schwedt TJ, Vargas B (2015) Neurostimulation for treatment of migraine and cluster headache. Pain Med 16:1827–1834
51. Clarke BM, Upton AR, Kamath MV, Al-Harbi T, Castellanos CM (2006) Transcranial magnetic stimulation for migraine: clinical effects. J Headache Pain 7:341–346
52. Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, Fischell RE, Ruppel PL, Goadsby PJ (2010) Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 9:373–380
53. Brighina F, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, Fierro B (2004) rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J Neurol Sci 227:67–71
54. Conforto AB, Amaro E Jr, Goncalves AL, Mercante JP, Guendler VZ, Ferreira JR, Kirschner CC, Peres MF (2014) Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. Cephalalgia 34:464–472
55. Misra UK, Kalita J, Bhoi SK (2013) High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. J Neurol 260:2793–2801
56. Teepker M, Hotzel J, Timmesfeld N, Reis J, Mylius V, Haag A, Oertel WH, Rosenow F, Schepelmann K (2010) Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. Cephalalgia 30:137–144
57. Magis D, Sava S, d'Elia TS, Baschi R, Schoenen J (2013) Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly(R) device in headache treatment: a survey of 2,313 headache sufferers in the general population. J Headache Pain. 14:95
58. Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gerard P, Magis D (2013) Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology. 80:697–704
59. Riederer F, Penning S, Schoenen J (2015) Transcutaneous supraorbital nerve stimulation (t-SNS) with the Cefaly(R) device for migraine prevention: a review of the available data. Pain Ther 4:135–147
60. Oshinsky ML, Murphy AL, Hekierski H Jr, Cooper M, Simon BJ (2014) Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia. Pain 155:1037–1042
61. Kinfe TM, Pintea B, Muhammad S, Zaremba S, Roeske S, Simon BJ, Vatter H (2015) Cervical non-invasive vagus nerve stimulation (nVNS) for preventive and acute treatment of episodic and chronic migraine and migraine-associated sleep disturbance: a prospective observational cohort study. J Headache Pain 16:101
62. Nesbitt AD, Marin JC, Tompkins E, Ruttledge MH, Goadsby PJ (2015) Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology. 84:1249–1253
63. Barbanti P, Grazzi L, Egeo G, Padovan AM, Liebler E, Bussone G (2015) Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. J Headache Pain 16:61
64. Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA (2014) Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. Cephalalgia 34:986–993
65. Grazzi L, Egeo G, Calhoun AH, McClure CK, Liebler E, Barbanti P (2016) Non-invasive vagus nerve stimulation (nVNS) as mini-prophylaxis for menstrual/menstrually related migraine: an open-label study. J Headache Pain 17:91
66. Silberstein SD, Calhoun AH, Lipton RB, Grosberg BM, Cady RK, Dorlas S, Simmons KA, Mullin C, Liebler EJ, Goadsby PJ, Saper JR (2016) Chronic migraine headache prevention with noninvasive vagus nerve stimulation: the EVENT study. Neurology. 87:529–538
67. Gaul C, Diener HC, Silver N, Magis D, Reuter U, Andersson A, Liebler EJ, Straube A (2016) Non-invasive vagus nerve stimulation for prevention and acute treatment of chronic cluster headache (PREVA): a randomised controlled study. Cephalalgia 36:534–546
68. Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, Liebler EJ, Rubenstein Engel E, Tepper SJ (2016) Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. Headache 56:1317–1332
69. Black RD, Rogers LL, Ade KK, Nicoletto HA, Adkins HD, Laskowitz DT (2016) Non-invasive neuromodulation using time-

varying caloric vestibular stimulation. IEEE J Transl Eng Health Med 4:2000310
70. Schytz HW, Barlose M, Guo S, Selb J, Caparso A, Jensen R, Ashina M (2013) Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. Cephalalgia 33:831–841
71. Schoenen J, Jensen RH, Lanteri-Minet M, Lainez MJ, Gaul C, Goodman AM, Caparso A, May A (2013) Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia 33:816–830
72. Tepper SJ, Rezai A, Narouze S, Steiner C, Mohajer P, Ansarinia M (2009) Acute treatment of intractable migraine with sphenopalatine ganglion electrical stimulation. Headache. 49:983–989
73. Ansarinia M, Rezai A, Tepper SJ, Steiner CP, Stump J, Stanton-Hicks M, Machado A, Narouze S (2010) Electrical stimulation of sphenopalatine ganglion for acute treatment of cluster headaches. Headache. 50:1164–1174
74. Barloese MC, Jurgens TP, May A, Lainez JM, Schoenen J, Gaul C, Goodman AM, Caparso A, Jensen RH (2016) Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. J Headache Pain 17:67
75. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ (2011) Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia 31:271–285
76. Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, Reed K, Narouze S, Mogilner A, Goldstein J, Trentman T, Vaisman J, Ordia J, Weber P, Deer T, Levy R, Diaz RL, Washburn SN, Mekhail N (2012) 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 32:1165–1179
77. Reed KL, Black SB, Banta CJ 2nd, Will KR (2010) Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. Cephalalgia 30:260–271
78. Reed KL, Will KR, Conidi F, Bulger R (2015) Concordant occipital and supraorbital neurostimulation therapy for hemiplegic migraine; initial experience; a case series. Neuromodulation 18:297–303 **(discussion 304)**
79. May A, Goadsby PJ (2001) Hypothalamic involvement and activation in cluster headache. Curr Pain Headache Rep 5:60–66
80. Bartsch T, Pinsker MO, Rasche D, Kinfe T, Hertel F, Diener HC, Tronnier V, Mehdorn HM, Volkmann J, Deuschl G, Krauss JK (2008) Hypothalamic deep brain stimulation for cluster headache: experience from a new multicase series. Cephalalgia 28:285–295
81. Fontaine D, Lazorthes Y, Mertens P, Blond S, Geraud G, Fabre N, Navez M, Lucas C, Dubois F, Gonfrier S, Paquis P, Lanteri-Minet M (2010) Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. J Headache Pain 11:23–31
82. Franzini A, Ferroli P, Leone M, Broggi G (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52:1095–1099 **(discussion 1099–1101)**
83. Leone M, Franzini A, Broggi G, Bussone G (2003) Hypothalamic deep brain stimulation for intractable chronic cluster headache: a 3-year follow-up. Neurol Sci 24(Suppl 2):S143–S145
84. Piacentino M, D'Andrea G, Perini F, Volpin L (2014) Drug-resistant cluster headache: long-term evaluation of pain control by posterior hypothalamic deep-brain stimulation. World Neurosurg 81:442.e411–442.e445
85. Magis D, Schoenen J (2012) Advances and challenges in neurostimulation for headaches. Lancet Neurol 11:708–719