New strategies for the treatment and prevention of primary headache disorders

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Abstract | The primary headache disorders, which include migraine, cluster headache and tension-type headache, are among the most common diseases and leading causes of disability worldwide. The available treatment options for primary headache disorders have unsatisfactory rates of efficacy, tolerability and patient adherence. In this Review, we discuss promising new approaches for the prevention of primary headache disorders, such as monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor, and small-molecule CGRP receptor antagonists. Neuromodulation approaches employing noninvasive or implantable devices also show promise for treating primary headache disorders. Noninvasive treatments, such as transcranial magnetic stimulation and transcutaneous peripheral nerve stimulation, are delivered by devices that patients can self-administer. Implantable devices targeting the occipital nerves, sphenopalatine ganglion or high cervical spinal cord are placed using percutaneous and/or surgical procedures, and are powered either wirelessly or by surgically implanted batteries. These new and emerging treatments have the potential to address unmet patient needs and reduce headache-associated disability.

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Collectively, headache disorders are the third leading cause of disability in the world in terms of disability-adjusted life years[1–4] (BOX 1). In the 2010 Global Burden of Disease Study, migraine had a global prevalence of 14.7%, compared with 20.1% for tension-type headache[1–3]. In the 2013 Global Burden of Disease Study, migraine accounted for over half of all years lost to disability that were attributed to neurological disorders[1–5]. Cluster headache, which affects 0.1–0.4% of the global population, is considered to be one the most severe types of pain that an individual can experience[6–11].

Currently available treatments for primary headache disorders have insufficient rates of efficacy and tolerability, and patients often do not adhere to the treatment[12]. Patients with refractory chronic migraine or refractory chronic cluster headache (BOX 2), in particular, have a dearth of effective treatment options.

In this Review, we discuss the new and emerging treatments that hold promise for addressing unmet patient needs and reducing disability caused by primary headache disorders. We first examine novel pharmacological treatments, such as therapeutics targeting calcitonin gene-related peptide (CGRP) or its receptor. We then consider new formulations of triptans and ergot derivatives for patient self-administration. Finally, we discuss both invasive and noninvasive neuromodulation approaches to treating primary headache disorders. Unless otherwise specified, the treatments that we review are either in trials or already available in clinical practice. The information reviewed here was found by performing a search for randomized controlled trials (RCTs) published in English between 1st June 2014 and 1st June 2016 (BOX 3).

Pharmacological treatments

There are a number of promising pharmacological treatments for primary headache disorders currently in clinical trials, including monoclonal antibodies (mAbs) targeting CGRP or its receptor, and small-molecule CGRP receptor antagonists. Several pharmacological treatments have already been approved for use in the USA (TABLE 1). Orexin receptor antagonists (BOX 4) have been subject to negative findings, and are not currently being pursued.

CGRP-targeted therapies

CGRP is a pain-signalling neuropeptide and potent vasodilator that is released from trigeminal sensory afferents and the spinal trigeminal nucleus[13–15] (FIG. 1). In individuals who are prone to migraine, exogenous CGRP infusion can trigger an attack[16,17]. CGRP is the best-validated

Key points

- Calcitonin gene-related peptide (CGRP) is the best-validated therapeutic target for migraine
- Monoclonal antibodies (mAbs) against CGRP or its receptor hold promise for migraine prevention, and small-molecule CGRP antagonists hold promise for acute and/or preventive treatment
- Four mAbs targeting CGRP or its receptor have been effective in phase II studies and are being studied in phase III trials for migraine prevention
- Non-oral systems to deliver triptans and dihydroergotamine mesylate for acute migraine treatment bypass hurdles posed by nausea, gastric stasis, and first-pass metabolism
- Noninvasive electrical and electromagnetic neurostimulators for primary headache disorders are available for clinical use, but regulatory approval varies by country, and patients might be required to cover costs
- For patients with intractable, medically refractory primary headache disorders, implantable neurostimulators targeting peripheral nerves, the sphenopalatine ganglion, and high cervical spinal cord are being studied

biomarker for migraine to date[18,19]: levels of the peptide are elevated in blood and saliva during migraine attacks (ictally) in patients diagnosed with episodic migraine, and between migraine attacks (interictally) in patients diagnosed with chronic migraine (FIG. 1). Patients with elevated CGRP levels are more likely to respond to triptans and dihydroergotamine mesylate (DHE) for acute migraine treatment, and to onabotulinumtoxinA for the treatment of chronic migraine[20–23].

CGRP or its receptor are now the focus of various clinical trials directed at preventing or treating migraine[24–28]. Currently, two main treatment avenues are being pursued: mAbs that target CGRP or its receptor, and small-molecule CGRP receptor antagonists.

Monoclonal antibodies. Targeting of CGRP with mAbs is a novel approach to headache prevention. Four such mAbs are in development, all of which have produced promising results in phase II studies and are currently in phase III clinical trials. Three of these mAbs bind CGRP, at differing locations on the peptide, and the fourth binds the CGRP receptor. The clinical significance of the differences between these mAbs is not yet known[15,29,30]. Although CGRP is a potent vasodilator, neither cardiovascular nor cerebrovascular adverse effects have been observed in any completed studies to date[31–34]. Anti-CGRP mAbs might act more quickly than existing migraine preventive treatments — a separation between treatment and placebo groups has been reported as early as 3 days after administration[35].

One of the most promising mAb treatments is LY2951742, which targets CGRP. All of the available CGRP-targeted mAbs are being developed solely for migraine prevention, but LY2951742 is also being studied for cluster headache prevention. Based on the unmet medical need of patients with cluster headache, the FDA granted LY2951742 fast-track status for expedited review to receive approval as a preventative treatment for the disorder. LY295142 was effective in one phase II RCT involving 218 participants with episodic migraine. Participants received a subcutaneous 150 mg dose of LY2951742 or a placebo every 2 weeks. The primary end point — reduction in monthly migraine headache days — was met during the third month of treatment, with a reduction of 4.2 headache days per month in the treatment group and 3.0 days per month in the placebo group. The 100% responder rate, which was defined as no migraine attacks during the 3-month trial, was also higher in the treatment group than in the placebo group. Injection site reactions were more common in the treatment group, but otherwise the treatment was well tolerated without serious adverse events[31]. Since the completion of the phase II trials, five phase III trials assessing LY2951742 in migraine or cluster headache have begun[36–40] (TABLE 2). LY2951742 is also being investigated in a lyophilized (freeze-dried) injectable formulation[41].

Intravenous administration of mAbs can reduce injection site reactions, which are a common adverse effect of subcutaneous mAb therapy. ALD403 is the only anti-CGRP mAb for which intravenous administration is being studied. ALD403 was effective in a phase II RCT that investigated the efficacy of the drug for prevention of episodic migraine[42]. During the trial, 163 patients with migraine received one intravenous infusion of either 1,000 mg ALD403 or placebo. The treatment group showed a reduction of 5.6 migraine headache days per month, compared with 4.6 days per month in the placebo group, and no infusion reactions were reported[32]. 12 weeks after the single infusion, the 100% responder

CGRP receptor
The calcitonin gene-related peptide (CGRP) receptor is a complex between the calcitonin receptor-like receptor and the receptor activity-modifying protein 1 (RAMP1). Expression of the CGRP receptor has been confirmed in the vasculature, the trigeminal ganglion, and the spinal trigeminal complex of the brainstem.

LY2951742
A fully humanized anti-calcitonin gene-related peptide IgG4 monoclonal antibody with a 28-day half-life (also known as galcanezumab).

Fast-track status
Fast-track status is granted by the FDA to investigational drugs anticipated to fill an unmet need in treating a serious condition.

ALD403
A genetically engineered, desialylated, humanized anti-calcitonin gene-related peptide IgG1 antibody with a 31-day half-life.

Box 1 | **Primary headache disorders**

- Cluster headache: Severe unilateral headaches lasting 15–180 min with a frequency of every 2 days to eight times a day, associated with ipsilateral autonomic symptoms and/or agitation
- Chronic cluster headache: Cluster headache cycles occurring for at least 1 year without remission of at least 1 month
- Episodic cluster headache: Cluster headache cycles occurring with at least 1 month of pain-free remission every 12 months
- Refractory cluster headache: See BOX 2 for the European Headache Federation (EHF) proposed definition
- Migraine: Headaches lasting 4–72 h which are often unilateral, pulsating, moderate to severe, and worsened by physical activity. They are associated with photophobia and phonophobia or nausea
- Chronic migraine: Migraine with or without aura with headaches 15 or more days a month, with 8 or more days a month experiencing migraines or using acute migraine treatment
- Episodic migraine: Migraine with or without aura, with fewer than 15 headache days per month
- Refractory chronic migraine: See BOX 5 for the EHF proposed definition
- Tension-type headache: Headaches that are often bilateral, non-pulsating, mild to moderate, and not worsened by physical activity. The headaches are not associated with nausea or photophobia and phonophobia.

Box 2 | **EHF criteria for refractory chronic cluster headache**

Refractory chronic cluster headache is not defined in the International Classification of Headache Disorders (ICHD)-3 beta criteria, but the European Headache Federation (EHF) has recently proposed criteria for this condition. The EHF recommended that refractory chronic cluster headache should be defined as ICHD 3-beta chronic cluster headache or probable cluster headache with at least three severe cluster headache attacks weekly after consecutive trials of at least three evidence-based preventive treatments have failed[140]. The proposed criteria are as follows:

A. Headache attacks fulfilling the ICHD-3 beta criteria for chronic cluster headache or probable cluster headache, plus criteria B–E below
B. At least three severe cluster headache attacks per week that affect patients' quality of life despite preventive or symptomatic treatment
C. Failed consecutive prophylactic treatment trials with at least three agents that showed efficacy over placebo in randomized controlled studies, used at the maximum tolerated dose over a sufficient period of time
D. Symptomatic chronic cluster headache is ruled out by negative investigation with brain MRI and magnetic resonance angiography, eventually supplemented with carotid CT angiograms or triplex carotid ultrasound
E. Not better accounted for by another ICHD-3 beta diagnosis

rate over 3 months was 16% in the treatment group versus 0% in the placebo group[32]. Two further RCTs — a phase II study for treatment of chronic migraine, and a phase I RCT evaluating quarterly subcutaneous and intramuscular dosing of ALD403 — have also reported positive preliminary results, although these findings have not yet been published[43]. One phase III RCT is currently underway[44] and another is planned (TABLE 2).

The anti-CGRP mAb TEV-48125, which is being studied as a monthly subcutaneous injection for prevention of episodic and chronic migraine, was effective in two phase IIb RCTs. In one of these trials, 297 participants with high-frequency episodic migraine received three monthly treatments of TEV-48125 at a dose of 675 mg or 225 mg, or a placebo. The 225 mg and 625 mg doses showed similar efficacy: the difference in reduction of migraine days per month between the treatment and placebo group was −2.8 days for 225 mg and −2.6 days for 625 mg. Apart from injection site effects, which occurred in 16% of participants in both treatment groups and 10% in the placebo group, TEV-48125 was well tolerated[19].

TEV-48125 was the first drug in its class to be shown to be effective in individuals with chronic migraine. In a phase IIb RCT involving 264 participants with chronic migraine, TEV-48125 treatment resulted in a significant reduction in headache hours per month in comparison with placebo[35]. Injection site reactions were reported, although they were mild and transient[33]. Phase III studies of TEV-48125 for the preventive treatment of episodic and chronic migraine are ongoing[45,46]. A long-term RCT studying the efficacy, tolerability and safety of the drug has an estimated completion date of autumn 2018 (REF. 47).

The CGRP receptor is also a therapeutic target for the treatment of primary headache disorders. Trials in the USA are investigating AMG 334 as a preventive drug for episodic and chronic migraine. A phase IIb RCT for the prevention of episodic migraine reported positive results for 70 mg AMG 334 (REF. 48). In this trial, 483 patients were randomly assigned to placebo, or to AMG 334 at a dose of 7 mg, 21 mg or 70 mg. The researchers reported a reduction of 3.4 migraine days per month in the 70 mg group from a baseline of 8.6 (±2.5), versus a reduction of 2.3 migraine days per month in the placebo group, from a baseline of 8.8 (±2.7). The two lower doses of AMG 334 did not significantly reduce migraine days. No serious treatment-related adverse events were reported during the study, and injection site reactions, which occurred in 5% of treated participants, were mild[34].

AMG 334 is being studied for prevention of episodic migraine in two international phase III RCTs[49,50] — both of which have an estimated completion date of Autumn 2016 — and a phase II chronic migraine prevention trial with an open label extension[51,52]. A further 5-year open-label extension study for AMG 334 is also ongoing[48,53]. Other ongoing studies include an RCT for episodic migraine prevention in Japan[54], and a trial investigating whether AMG 334 affects treadmill exercise time in individuals with stable angina[55] (TABLE 2).

CGRP receptor antagonists. Small-molecule CGRP receptor antagonists have been investigated for both acute migraine treatment and migraine prevention. Several previously studied small-molecule CGRP receptor antagonists were effective in phase II and III trials, but their development was halted owing to hepatotoxicity, inability to develop an oral formulation, or other unknown reasons[25–28]. Following the successes in phase II and III trials, several new small-molecule CGRP receptor antagonists have been developed and are now being studied for migraine treatment. Ubrogepant is one such drug that is currently in trials. In its phase 2b RCT, it outperformed placebo in 2 h pain freedom but not 2 h headache response[56]. Phase III studies of ubrogepant are expected to begin in the second half of 2016. Phase II trials of MK-8031, a CGRP receptor antagonist, for migraine prevention are also expected to begin in 2016. A host of other oral CGRP receptor antagonists for treatment of acute migraine are currently in development, and are anticipated to enter phase I trials in 2016.

Other pharmacological treatments

Established migraine treatments such as ergot derivatives, triptans and ditans are believed to exert their effects via serotonin (5-hydroxytryptamine, or 5-HT) receptors. Triptans are standard of care for the acute treatment of

TEV-48125
A fully humanized anti-calcitonin gene-related peptide IgG2a monoclonal antibody with a half-life of 40–48 days (previously known as LBR-101).

AMG 334
A human IgG2 monoclonal antibody that is targeted against the calcitonin gene-related peptide receptor. AMG 334 has a half-life of 21 days.

Ubrogepant
An orally administered small-molecule calcitonin gene-related peptide antagonist for the acute treatment of migraine (also known as MK-1602).

MK-8031
An orally administered small-molecule calcitonin gene-related peptide antagonist for the prevention of migraine.

Acute treatments
Treatments that are used as needed while experiencing a headache, with the purpose of aborting the headache. These treatments include simple analgesics, triptans, and ergot derivatives such as dihydroergotamine mesylate.

Box 3 | **Search criteria**

A search for randomized controlled trials published in English between 1st June 2014 and 1st June 2016 was performed in PubMed. The search term used was "(migraine AND prevention) OR (migraine AND treatment) OR (cluster headache AND prevention) OR (cluster headache AND treatment)". We also searched the reference lists of identified articles for further relevant papers.

A search for "migraine" or "cluster headache" interventional studies, limited to open studies and active but not recruiting studies, between 1st June 2014 and 1st June 2016, was performed in ClinicalTrials.gov. Results from these searches were further searched in PubMed and ClinicalTrials.gov.

We included articles and clinical trials concerning novel pharmaceuticals, new formulations of triptans or ergot derivatives for patient self-administration, and noninvasive and implantable neuromodulation devices. Owing to space limitations, we excluded articles and clinical trials concerning medications marketed for non-headache indications but now being studied for primary headache disorders; single isomer drugs or combination pills of medications already in use for primary headache disorders; dietary, nutraceutical and health food studies; complementary and alternative medicine, integrative medicine, and osteopathic manipulation studies; lifestyle, educational or psychological interventions; emergency room, physician office or infusion centre interventions; repetitive transcranial magnetic stimulation studies; novel delivery devices for physician injections of local anaesthetics, steroids, alcohol or botulinumtoxins; deep brain stimulation; and trigger site deactivation and nerve decompression surgery studies.

migraine and cluster headache, but are contraindicated in patients at risk of cardiovascular or cerebrovascular events because of concerns over vasoconstrictive effects. The 5-HT_{1F} receptor is found throughout the peripheral and central trigeminovascular system, but 5-HT_{1F} agonists (ditans) do not cause vasoconstriction *in vitro*, making this receptor an intriguing target for migraine treatment.

Non-triptan serotonin receptor agonists. Ditans hold promise for acute migraine treatment without the vasoconstriction concerns associated with triptans (5-$HT_{1B/1D}$ agonists). LY334370, a 5-HT_{1F} receptor agonist, showed promise in a phase II RCT; its development was halted, however, because of hepatotoxicity in canine trials[57]. Another 5-HT_{1F} receptor agonist, lasmiditan, was effective for acute migraine treatment in two phase IIb studies[58–60], with oral doses of 200 mg and 400 mg surpassing placebo with regard to pain freedom at 2 h. No adverse cardiovascular effects or triptan chest symptoms were reported in the lasmiditan phase IIb RCTs, although, dose-dependent adverse effects have been reported, most markedly dizziness, but also paraesthesia, fatigue and nausea[59,61]. The SAMURAI study[62], a phase III trial that finished in 2016, showed positive efficacy results for 100mg and 200mg doses of lasmiditan. Over 80% of participants in the study had cardiovascular risk factors but no cardiovascular events were reported. SPARTAN, a planned phase III trial, will evaluate the efficacy of lasmiditan for the treatment of a single migraine attack in people with 3–8 migraine days monthly. The SAMURAI trial excluded patients with known coronary artery disease, clinically significant arrhythmia or uncontrolled hypertension; no such restrictions were made in the enrolment for SPARTAN. The estimated primary completion date is June 2017 for SPARTAN.

Triptans and ergot derivatives. Onzetra Xsail (Avanir Pharmaceuticals, Inc., Aliso Viejo, California, USA) is a bidirectional, breath-powered intranasal delivery system for powdered sumatriptan (TABLE 1; FIG. 2). During phase I trials, Onzetra Xsail achieved faster absorption and lower peak and total systemic exposure to sumatriptan than did the oral delivery route[63]. In the placebo-controlled phase III RCT TARGET, Onzetra Xsail demonstrated improved headache relief and pain freedom at 2 h, compared with placebo[64]. It was also better than placebo in providing sustained pain relief and pain freedom at 24 and 48 h. In the phase IIIb COMPASS trial[65] — a double-dummy, crossover, comparative effectiveness study comparing 22 mg Onzetra Xsail with 100 mg oral sumatriptan — Onzetra Xsail improved summed pain intensity differences up to 30 min post-dose. The reported incidence of atypical triptan sensations was also lower in the Onzetra Xsail group. Onzetra Xsail outperformed oral sumatiptan in pain relief and pain freedom up to 90 min post-dose, but after this time point no difference was observed between the two drugs. Onzetra Xsail was approved by the FDA in January 2016, and became available for prescription in the USA in May 2016.

ZEMBRACE SymTouch (Promius Pharma LLC, a subsidiary of Dr. Reddy's Laboratories, Ltd, Hyderabad, India) is a single-dose, disposable, ready-to-use subcutaneous autoinjector prefilled with 3 mg sumatriptan, which was launched for the acute treatment of migraine in April 2016. Most other sumatriptan autoinjectors deliver 4 mg or 6 mg of sumatriptan, but these higher doses are associated with intolerable adverse events in some patients. ZEMBRACE SymTouch, which can be used hourly up to four times daily, also uses a smaller needle (29 gauge) than other autoinjectors. Two phase II trials — one for rapidly escalating migraine[66] and the other for medication overuse headache[67] — and one phase III study for episodic migraine[68] are currently investigating ZEMBRACE SymTouch. The autoinjector might also be useful off-label for patients with cluster headache.

The Zecuity iontophoretic transdermal delivery system for sumatriptan (Teva Pharmaceuticals, Ltd, Petah Tikva, Israel) became available for prescription in the USA in September 2015 (TABLE 1). The Zecuity patch is applied to the skin and, once activated, delivers 6.5 mg of sumatriptan over a fixed 4 h period. This delivery method bypasses the gastrointestinal system and, therefore, first-pass metabolism by delivering sumatriptan transdermally into the subcutaneous space via a battery-driven electrical current[69,70]. In June 2016, the FDA announced that it had initiated an investigation into the risk of burns and scarring due to the product. Soon afterwards, Teva Pharmaceuticals announced that it would voluntarily halt sales, marketing and distribution of the product in the USA[71]. Zecuity had not been made available in any countries outside the USA.

Dihydroergotamine for oral inhalation was found to be safe and effective in its phase III trial, FREEDOM-301 (REF. 72). Orally inhaled dihydroergotamine maintains its efficacy late in the course of migraine and after the development of cutaneous allodynia. This finding is in contrast to triptans, which tend to be most effective early

Paraesthesia
An abnormal sensation, often described as a 'pins and needles' feeling, that can be caused by medications or by damage, compression, or stimulation of peripheral nerves.

Double-dummy
A double-dummy study is a form of double-blind study that is used when the two treatments being studied cannot be made to appear identical. For example, it can be used to compare an inhaled medication with an oral medication. All participants are administered two treatments — one inhaled and one oral. Participants are randomly assigned to receive either the active inhaled treatment and placebo oral treatment or the placebo inhaled treatment and active oral treatment.

Atypical triptan sensations
Atypical triptan sensations are often reported following the use of triptans. Atypical triptan sensations include tightness and tingling in the chest, limbs and face. They are benign, but can be mistaken for much more serious conditions.

Table 1 | **Pharmacological treatments for primary headache disorders: approved and in development**

Name	Indications	Availability	Benefits	Notes	Refs
LY2951742	Anti-CGRP mAb for migraine and cluster headache prevention	Phase III studies ongoing	May be more effective and better tolerated than current preventive medications	Only drug in its class currently in trials for cluster headache (all four mAbs are in trials for migraine)	37–41
ALD403	Anti-CGRP mAb for migraine prevention	Phase III studies ongoing	May be more effective and better tolerated than current preventive medications	Only drug in its class being studied for intravenous delivery or 3-monthly dosing	44
TEV-48125	Anti-CGRP mAb for migraine prevention	Phase III studies ongoing	May be more effective and better tolerated than current preventive medications	Only drug in its class with published phase II trial data for treatment of chronic migraine (all mAbs have been trialled in episodic migraine)	45,46
AMG 334	Anti-CGRP receptor mAb for migraine prevention	Phase III studies ongoing	May be more effective and better tolerated than current preventive medications	Only drug in its class to target CGRP receptor (the others target CGRP)	49,50,54
Ubrogepant	Small-molecule CGRP antagonist for acute migraine	Positive phase IIb results; phase III studies are anticipated	May be effective in triptan non-responders	Previous small-molecule CGRP antagonist studies revealed hepatotoxicity	56
MK-8031	Small-molecule CGRP antagonist for migraine prevention	Phase II studies anticipated	Oral medication with short half-life; may be more appealing than anti-CGRP mAbs to patients averse to needles or worried about potential adverse effects	Previous small-molecule CGRP antagonist studies revealed hepatotoxicity	159
Lasmiditan	5HT-1F receptor agonist for acute migraine	Effective in phase III SAMURAI study (unpublished data); phase III SPARTAN trial ongoing	May avoid typical triptan adverse effects and be safe for patients with cardiovascular and cerebrovascular risk factors	Whereas triptans target 5-HT-1B/1D receptors, ditans such as lasmiditan target the 5-HT-IF receptor and do not cause vasoconstriction	61
Onzetra Xsail (Avanir Pharmaceuticals, Inc., Aliso Viejo, California, USA)	Intranasal sumatriptan for acute migraine	Approved in the USA, marketing began May 2016	Fast-acting, bypasses GI tract	Can be considered off-label for acute cluster headache treatment	63–65, 149,150
ZEMBRACE SymTouch (Promius Pharma LLC, a subsidiary of Dr. Reddy's Laboratories, Ltd, Hyderabad, India)	Subcutaneous sumatriptan autoinjecto for acute migraine	Approved in the USA, marketing began in May 2016	Fast-acting, bypasses GI tract	Can be considered off-label for acute cluster headache treatment; can be used four times a day to treat cluster headache	66–68
Zecuity (Teva Pharmaceuticals, Ltd, Petah Tikva, Israel)	Transdermal sumatriptan for acute migraine	Previously approved and marketed in the USA, now suspended	Long-acting, bypasses GI tract	Marketing suspended June 2016 because of burns and scarring	69–71, 151–153
Dihydroergotamine for oral inhalation	Orally inhaled dihydroergotamine mesylate for acute migraine	Rejected by FDA three times due to manufacturing concerns	Safe and effective in phase III study for migraine treatment. Effective in prolonged migraine and migraine with cutaneous allodynia	Might be effective in acute cluster headache, but has encountered manufacturing concerns related to canister filling, uniformity of contents and actuation	79–82
ZP-Zolmitriptan	Zolmitriptan microneedle patch for acute migraine	Phase II/III trial planned for 2016	Rapid absorption in a phase I study	Phase II study anticipated	154,155
CVT-427	Inhaled formulation of zolmitriptan for acute migraine	In clinical trials	Aerodynamic design to rapidly deliver a consistent dose of zolmitriptan	Phase I study demonstrated rapid T_{max} of 0.17 h (REF. 78)	156–158
Ibudilast	Migraine prevention	Ineffective in medication overuse phase II trial; awaiting results from chronic migraine phase II study	Novel approach for migraine prevention	Has been used in Japan for non-headache indications since the 1970s	160–165

CGRP, calcitonin gene-related protein; GI, gastrointestinal tract; mAb, monoclonal antibody; RCT, randomized controlled trial, Tmax, the time at which a drug reaches its maximum concentration in the plasma.

Cutaneous allodynia
In cutaneous allodynia, central sensitization to pain causes normally non-noxious tactile stimuli to skin (such as showering, shaving, brushing the hair or wearing tight clothing) to be experienced as painful.

Status migrainosus
A migraine attack lasting more than 72 h.

Box 4 | Orexin receptor antagonists

Orexin A and B are neuropeptides that are released by the hypothalamus[141,142]. They act via orexin receptors 1 and 2, and are involved in appetite and wakefulness. The interaction between migraine and sleep, including the role of sleep in aborting migraines, prompted the hypothesis that orexin antagonists might be a suitable target for migraine therapies[143,144]. With this hypothesis in mind, researchers studied filorexant, an orexin receptor 1 and 2 antagonist, for migraine prevention[145]. In an exploratory phase II randomized control trial, filorexant was administered nightly to individuals with episodic migraine, but it did not significantly reduce mean monthly migraine or headache days[146]. Since the publication of these negative data, no other trials of filorexant or any other orexin receptor antagonists have been registered with ClinicalTrials.gov.

in migraine and before the development of cutaneous allodynia[73–75]. Dihydroergotamine for oral inhalation seems to be safer and better tolerated than intravenous dihydroergotamine and, notably, seems to be safe and well tolerated for chronic use, and in people with comorbid asthma[76–82].

Orally inhaled dihydroergotamine would provide a fast-acting, easily self-administered treatment for use as a rescue treatment in prolonged migraine and status migrainosus. However, the FDA has rejected approval of dihydroergotamine for oral inhalation on three occasions owing to manufacturing concerns related to canister filling, uniformity of contents and actuation. Development is ongoing, and an application for FDA approval will presumably be submitted once the manufacturing concerns are resolved.

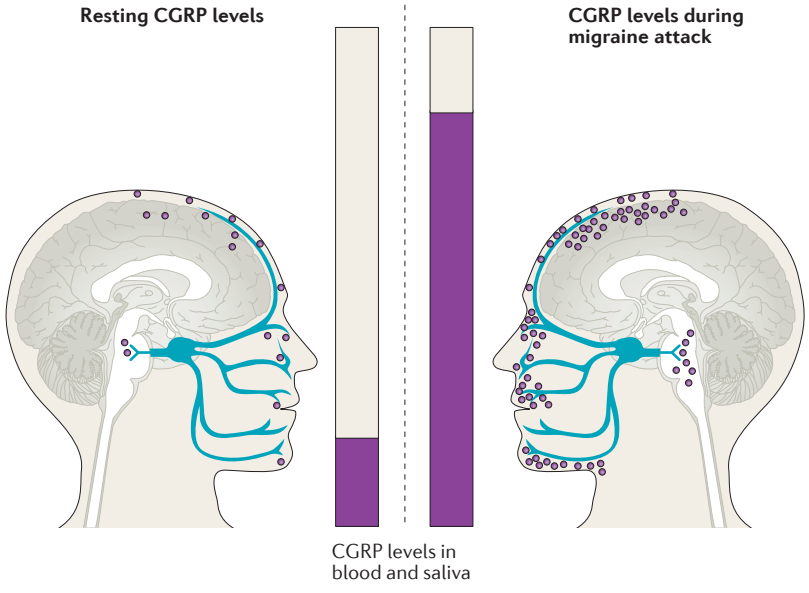

Figure 1 | **CGRP levels during migraine attacks.** Calcitonin gene-related peptide (CGRP) is released from trigeminal sensory afferents and the spinal trigeminal nucleus. During migraine attacks, CGRP levels in the blood and saliva are increased. Administration of exogenous CGRP can induce migraine. Several therapeutics that target the CGRP pathway to treat primary headache disorders are in development.

Neuromodulation

Neuromodulation treatments for primary headache disorders include noninvasive treatments and implantable devices. Noninvasive treatments are delivered by devices that patients can purchase or rent and can self-administer on a scheduled or as-needed basis. Implantable devices are placed using percutaneous and/or surgical procedures, and are powered either wirelessly or by surgically implanted batteries. The settings of these devices can be changed remotely. Treatment targets include the cerebral cortex, cranial nerves, occipital nerves (including trigeminal nerve branches and vagus nerves), and the trigeminal nucleus caudalis in the high cervical spinal cord.

Noninvasive neuromodulation treatments

Transcranial magnetic stimulation. Transcranial magnetic stimulation (TMS) is a noninvasive technique that uses fluctuating magnetic fields to induce a current in targeted areas of the cerebral cortex. Animal model studies have shown that TMS inhibits both cortical spreading depression and nociceptive trigeminothalamic neurons[83,84]. TMS can be delivered in repetitive pulses or single pulses. Repetitive TMS is a clinic-based procedure, and various protocols, including targeting of different areas of cortex and use of different frequencies of stimulation, have been trialled with mixed results[85–87].

The benefit of single-pulse TMS is that the patient can be prescribed the device for self-administration at home. SpringTMS (eNeura Inc., Sunnyvale, California, USA) is a portable single-pulse TMS device that is approved in the USA for the acute treatment of migraine with aura. The device has also been granted a Conformité Européenne mark in the European Union for the acute and preventive treatment of migraine with or without aura (FIG. 3a). In the pivotal RCT of single-pulse TMS for the acute treatment of migraine with aura, 267 participants received two pulses to the occiput, 30 s apart, of either active or sham stimulation, within 1 h of aura onset. Patients receiving the treatment were more likely to be pain-free at 2 h (39%) than were sham-treated patients (22%)[88].

Single-pulse TMS has also been investigated in a UK open-label, post-marketing trial including 190 participants with episodic or chronic migraine: 59 with episodic migraine and 131 with chronic migraine. In contrast to the pivotal RCT, this trial did not exclude migraine patients without aura. Participants were instructed to use the device acutely, administering up to four pulses every 15 min for 1–2 h or until migraine symptoms resolved. 62% of participants reported reduction or alleviation of pain, and 64% reported reduction in associated migraine symptoms, such as photophobia, phonophobia or nausea. Acute migraine medication use was reduced by an average of 8.5 monthly days in 119 of the 164 participants who reported use of this medication. Mean headache days per month were reduced in both the episodic migraine population (from 12 to 9 days) and the chronic migraine population (from 24 to 16 days). No serious adverse events were reported, but in total 55% of participants discontinued use of the device owing to

Table 2 | **Phase III randomized controlled trials of monoclonal antibodies against CGRP or its receptor**

Study	Primary efficacy outcomes	Administration route, frequency and duration	Study groups	Sample	Estimated primary completion	Location
LY2951742						
EVOLVE-1 (REF. 36)	Reduction of MD/M	SC, every month for 6 months	Two doses and placebo	825 patients with episodic migraine	February 2017	USA
EVOLVE-2 (REF. 37)	Reduction of MD/M	SC, every month for 3 months	Two doses and placebo	825 patients with episodic migraine	June 2017	USA
REGAIN[38]	Reduction of MD/M	SC, every month weeks for 2 months	Two doses and placebo	825 patients with chronic migraine	February 2017	USA
Episodic cluster headache study[39]	Reduction of weekly cluster attacks	SC, every month for 6 months	One dose and placebo	162 patients with episodic cluster headache	December 2016	North America and Europe
Chronic cluster headache study[40]	Reduction of weekly cluster attacks	SC, every month weeks for 3 months	One dose and placebo	162 patients with chronic cluster headache	November 2016	USA and Europe
ALD403						
PROMISE 1 (REF. 44)	Difference in responder rate	IV, one dose with primary outcome at 12 weeks	Three doses and placebo	600 patients with episodic migraine	January 2017	USA
PROMISE 2 (Episodic migraine)	Not announced	Not announced	Not announced	Not announced	Not announced	Not announced
TEV-48125						
Episodic migraine study[45]	Reduction of MD/M	SC, every 28 days for 12 weeks	Two doses and placebo	786 patients with episodic migraine	September 2017	USA and Israel
Chronic migraine study[46]	Reduction of HD/M	SC, every 28 days for 12 weeks	Two doses and placebo	1020 patient with chronic migraine	September 2017	North America, Europe and Israel
AMG 334						
STRIVE[49]	Reduction of MD/M	SC, every month for 6 months	Two doses and placebo	852 patients with episodic migraine	August 2016	North America and Europe
ARISE[50]	Reduction of MD/M	SC, every month for 3 months	One dose and placebo	540 patients with episodic migraine	July 2016	USA and Europe
Chronic migraine study[51]	Reduction of MD/M	SC, every month for 3 months	Two doses and placebo	667 patients with chronic migraine	February 2016	North America and Europe

CGRP, calcitonin gene-related protein; HD/M, headache days per month; IV, intravenous; MD/M, migraine days per month; SC, subcutaneous.

problems including no benefit or inadequate benefit (49 patients), migraine improved or resolved (12 patients), and adverse effects (two patients)[89].

The ESPOUSE trial[90], a US-based, prospective, open-label, post-marketing study for individuals with migraine with or without aura, is an ongoing study investigating single-pulse TMS for migraine prevention and acute treatment. Although SpringTMS is now available for rental by prescription in the UK and the USA, the cost of the device can be prohibitive for many patients, especially considering that it might not be covered by insurance.

Transcranial direct current stimulation. Transcranial direct current stimulation (tDCS) can modulate cortical activity via anodal (activating) or cathodal (inhibitory) stimulation that is delivered using noninvasive, portable and affordable devices[91] (FIG. 3b). In a single-centre RCT performed in Thailand, 42 patients with episodic migraine were randomly assigned to receive 1 mA anodal tDCS or sham stimulation. Treatments lasted for 20 min and were delivered daily for 20 consecutive days, with the anode placed over the left primary motor cortex. Following treatment, the group receiving active tDCS experienced fewer migraine days than did the sham group at weeks 4 and 8. The active treatment group also used less abortive medication and reported lower pain intensity than did the sham group[92]. Another small, sham-controlled RCT investigating 2 mA anodal tDCS for the treatment of chronic migraine also reported a reduction in headache intensity in the treatment group, although no change in headache frequency was reported[93]. In an open-label, single-arm study investigating 15 min treatments of 1 mA anodal tDCS over the visual cortex for migraine without aura, investigators reported a significant reduction in migraine frequency, migraine days, attack duration, and acute treatment[94]. Two RCTs studying cathodal tDCS over the visual cortex found no difference in headache frequency between active and sham groups[94,95]. Several tDCS studies for migraine prevention are planned or ongoing[96–99].

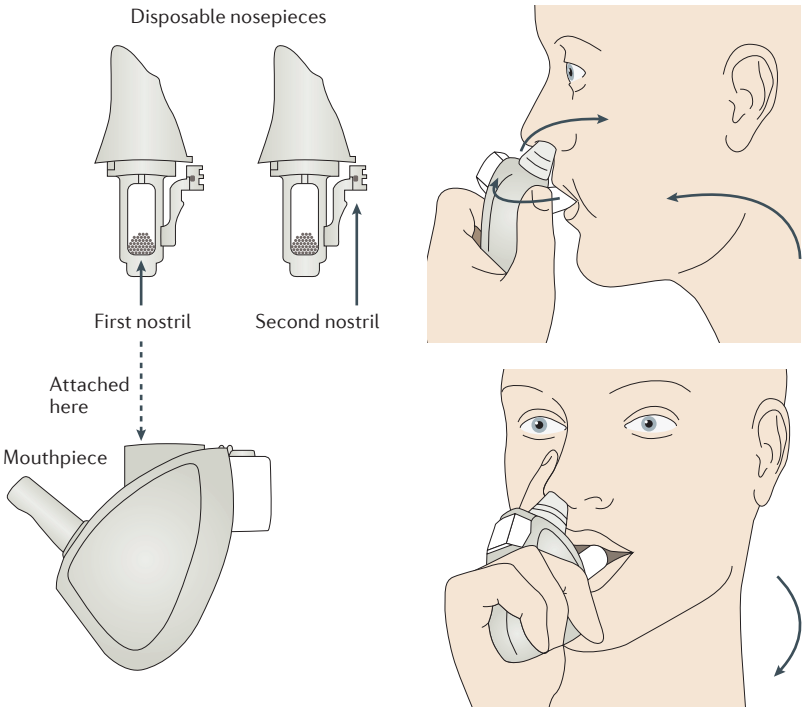

Figure 2 | **Nasal administration of sumatriptan via Onzetra Xsail.** Onzetra Xsail (Avanir Pharmaceuticals, Inc., Aliso Viejo, California, USA) is a breath-powered nasal drug delivery system that delivers two 11 mg doses of sumatriptan to the nasal cavity. Drug delivery is triggered by oral exhalation into the apparatus, which expels the powdered drug into the nasal cavity while simultaneously causing the soft palate to elevate. This manoeuvre increases absorption across the nasal mucosa, especially in the upper posterior nasal cavity, where absorption is best, and also prevents the drug from entering the gastrointestinal tract via the oropharynx — a common occurrence when using liquid nasal sprays[149,150].

Noninvasive pericranial peripheral nerve stimulators. The Cefaly device (Cefaly Technology, Grâce-Hollogne, Belgium) delivers transcutaneous electrical stimulation to both supraorbital nerves, and is available for purchase with a prescription in the USA and without a prescription in Australia, Canada, Europe and the UK (FIG. 3c). In a pivotal RCT for prevention of episodic migraine, which included 67 participants with two or more migraine attacks monthly, treatment with Cefaly reduced monthly migraine days by 30% from baseline to the third month of treatment. Sham treatment did not significantly reduce migraine days per month[100,101]. In a post-marketing survey of 2,313 Cefaly users, 54% were satisfied and willing to purchase the device[102]. In our experience, however, many patients find the paraesthesias that this device induces in the supraorbital distribution to be uncomfortable. Cefaly is currently being studied for acute treatment of episodic or chronic migraine in a double-blind RCT[103], as well as in an open-label study for prevention of chronic migraine[104].

Another noninvasive pericranial peripheral nerve stimulator that combines occipital nerve and supraorbital nerve transcutaneous electrical stimulation is in clinical trials. The device was recently studied for acute migraine treatment in 40 participants with episodic migraine in a prospective, single-blind, placebo-controlled RCT[105], but the results have not yet been reported.

Noninvasive vagal nerve stimulators. The gammaCore device (electroCore LLC, Basking Ridge, New Jersey, USA) is a handheld device that provides transcutaneous stimulation of the cervical branch of the vagus nerve (FIG. 3d). The device is currently approved for use in Australia, Brazil, Canada, Colombia, Europe, India, Malaysia, New Zealand and the UK. The UK National Institute for Health and Care Excellence published an interventional procedures programme supporting the safety of gammaCore and its use in the UK National Health Service in August 2015 (REF. 106).

Noninvasive vagal nerve stimulation (nVNS) has been studied in three cluster headache studies. Two studies — a nonblinded study without a sham control[107], and a sham-controlled trial[108] — were conducted in Europe, and one sham-controlled study was conducted in the USA[109].

In the nonblinded, European RCT for the acute and preventive treatment of chronic cluster headache, 93 people were randomly assigned to transcutaneous nVNS plus standard care, or standard care alone. Patients in the nVNS group self-administered three 90 s stimulations twice daily for preventive treatment, as well as optional acute treatments for cluster attacks. The number of cluster attacks was reduced more in the nVNS group (on average 5.9 fewer attacks per week, down from an average of 16.8 attacks per week over 4 weeks before enrolment) than in the control group (2.1 fewer attacks per week, down from an average of 18.5 attacks per week over the 4 weeks before enrolment). The ≥50% response rate — that is, the proportion of participants with a ≥50% reduction in cluster headache attacks per week — was significantly higher in the nVNS than in the control group (40.0% versus 8.3%). The patients receiving nVNS also considerably reduced their use of acute cluster headache treatments, such as sumatriptan injections and oxygen therapy. The authors reported that optional use of nVNS for acute cluster headache treatment in this study had no effect on attack duration or pain intensity[110].

In the ACT1 study, a double-blind, sham controlled study in the USA, showed nVNS did not meet its primary efficacy outcome. A subgroup analysis, however, showed that nVNS was effective for the acute treatment of episodic cluster headache but not for chronic cluster headache[111].

nVNS is also being studied for both acute and preventive treatment of migraine. An open-label, single-arm, multicentre Italian study, which included 50 patients with migraine, investigated nVNS for acute treatment of high-frequency or chronic migraine. At 2 h after treatment, patients experienced a pain relief rate (≥50% reduction in pain) of 51% and a pain-free rate of 23%[112]. These results replicated those of a previous single-centre, open-label, single-arm US pilot study in which 30 patients self-administered nVNS for acute migraine treatment[113].

The EVENT pilot study, which was the first prospective, multicentre, double-blind, sham-controlled pilot study of nVNS for prevention of chronic migraine, published its findings in July 2016. The study investigated

preventive use of nVNS for chronic migraine prevention in 59 patients. The 2-month randomized phase was followed by a 6-month open-label phase. EVENT was not powered to assess efficacy, and the difference between groups at 2 months was not significant. After 2 months, headache days per month were reduced in the nVNS group from 20.8 to 19.4, and in the sham group from 22.3 to 22.0. During the open-label phase, the researchers reported a mean reduction of 3.6 headache days per month in the nVNS group from an average baseline of 20.8 at the 8-month time point. Adverse events were mostly transient and mild to moderate, and the authors concluded that the intervention was well tolerated without safety issues[114]. However, a small number of patients have reported local discomfort, tonic muscle contraction, fatigue, palpitations and/or cervical muscle contractions following nVNS[115]. Larger trials investigating nVNS for acute treatment of migraine and prevention of episodic migraine are ongoing (TABLE 3).

The NEMOS device (Cerbomed, Erlanger, Germany) transcutaneously stimulates the auricular branch of the vagus nerve (FIG. 3e). In a single-centre study, people with chronic migraine were randomly assigned to receive a daily self-administered 4 h treatment consisting of either 25 Hz or 1 Hz nVNS stimulation. The 1 Hz stimulation protocol group experienced a more marked reduction in headache days (–7.0 headache days per month, from an average baseline of 19.1) than did the 25 Hz stimulation protocol group (–3.3 headache days per month, from an average baseline of 19.2). Interestingly, the researchers wrote that the 1 Hz stimulation was intended to serve as the sham stimulation. Mild to moderate adverse events such as pain, paraesthesias and pruritus (itch) were common. Treatment-related adverse events leading to discontinuation were reported in 18% of participants in the group receiving 1 Hz VNS and 4% in the 25 Hz VNS group. The discontinuations were mostly due to ulceration at the stimulation site, which was experienced by

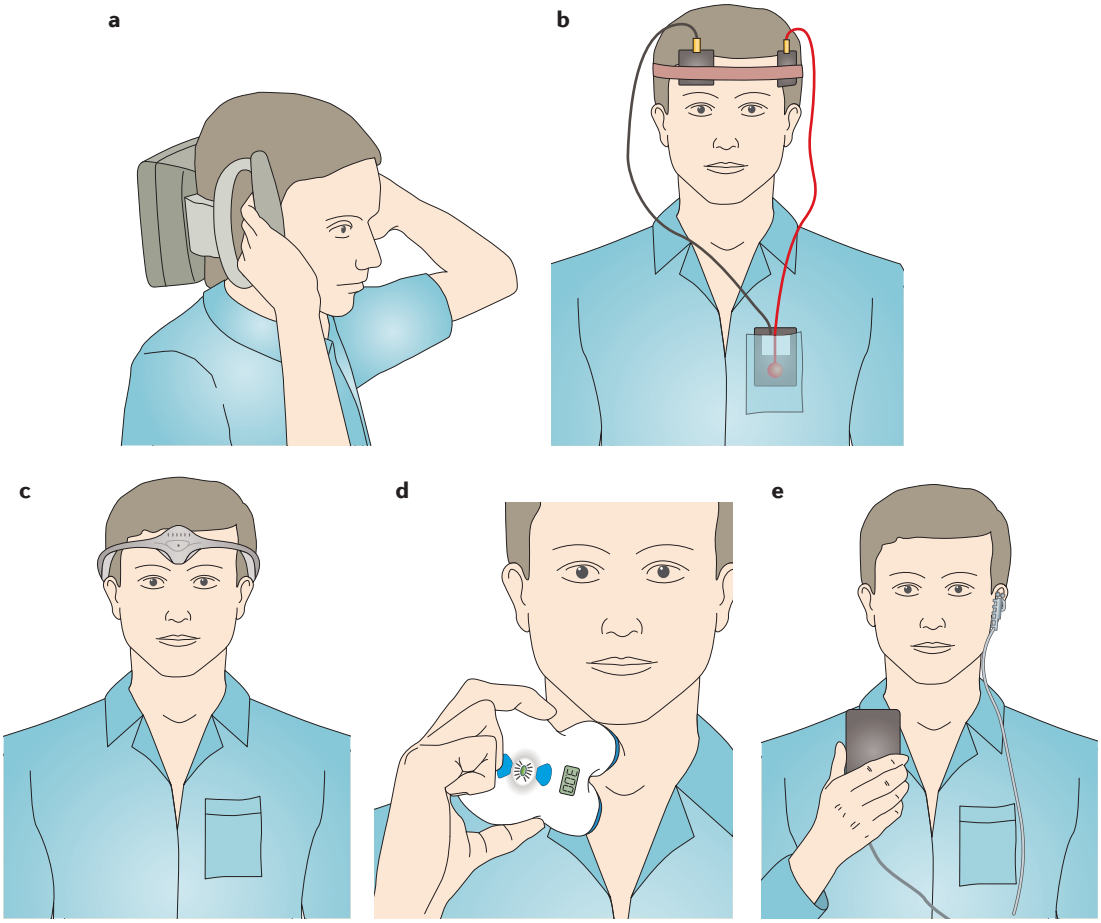

Figure 3 | **Non-invasive neuromodulation treatments. a** | SpringTMS (eNeura Inc., Sunnyvale, California, USA) is a portable transcranial magnetic stimulation device that is used to treat migraine with aura. **b** | Transcranial direct current stimulation devices are noninvasive, portable treatments that deliver an electrical current via a cathode and an anode that are strapped to the patient's head. **c** | The Cefaly device (Cefaly Technology, Grâce-Hollogne, Belgium) is a noninvasive pericranial peripheral nerve stimulator that is placed over the forehead. The smaller Cefaly II is now available in the USA. **d** | The gammaCore device (electroCore LLC, Basking Ridge, New Jersey, USA) is a handheld noninvasive vagal nerve stimulator. **e** | The NEMOS device (Cerbomed, Erlanger, Germany) is a portable transcutaneous stimulator that targets the auricular branch of the vagus nerve. An ear electrode is worn in contact with the skin of the concha, similar to a hearing aid, and the device is powered by a handheld, battery powered electrical stimulator.

Table 3 | **Neuromodulation devices for primary headache disorders: approved and in development**

Name	Description	Indications	Availability	When to consider	Ongoing studies	Refs
SpringTMS (eNeura Inc., Sunnyvale, California, USA)	Single-pulse occipital transcranial magnetic stimulation	Acute treatment of migraine with aura in the US; acute and preventive treatment of migraine with or without aura in the EU	Available by prescription for rent in the UK and USA	Patients with side effects to current treatments, cardiovascular risk factors, and frequent migraines who are at risk for medication overuse headache. May be helpful for patients with prominent visual aura	Acute treatment of migraine without aura and migraine prevention	90
Cefaly (Cefaly Technology, Grâce-Hollogne, Belgium)	Transcutaneous electrical nerve stimulation for trigeminal branches	Migraine prevention	Available for puchase with a prescription in the USA and without a prescription in Australia, Canada, Europe and the UK	Patients averse to oral or percutaneous preventive medications	Acute migraine treatment	100,101
OSTNS Neurostimulator (Neurolief Ltd, Herzliya, Israel)	Transcutaneous pericranial peripheral nerve stimulator	Acute migraine treatment	Not available	Potential alternative or adjuvant to pharmacological acute treatments	Results of RCT of 40 patients have not yet been reported	105
Medtronic (Fridley, Minnesota, USA and Dublin, Ireland)	Implantable occipital nerve stimulator	Medically intractable chronic migraine and cluster headache	Available for implantation, but obstacles to insurance coverage exist	Controversial; patients with medically refractory headache disorders	The ICON study, a double-blind RCT for chronic cluster headache, is ongoing.	118,119
Precision System (Boston Scientific Corporation Marlborough, Massachusetts, USA)	Implantable occipital nerve stimulator	Refractory chronic migraine	Available for implantation, but obstacles to insurance coverage exist	Controversial; patients with medically refractory headache disorders	The OPTIMISE trial, a double-blind RCT for chronic migraine, is ongoing	127
The StimRelieve Halo Migraine System (Stimwave LLC, Fort Lauderdale, Florida, USA)	Percutaneously placed leads which are powered by a wireless external unit	Treatment of migraine	Available for implantation, but obstacles to insurance coverage exist	Controversial; patients with medically refractory headache disorders	Two RCTs are planned	128,129
The Pulsante SPG Neurostimulator (Autonomic Technologies, Inc., Redwood City, California, USA)	A tiny, wireless, remote-controlled SPG stimulator	Migraine and chronic cluster headache	Approved in Europe for the treatment of primary headache disorders	Controversial; patients with medically refractory headache disorders	Pathway CH-2 study for chronic cluster headache and Pathway M-1 study for chronic migraine	132,133
GammaCore (electroCore LLC, Basking Ridge, New Jersey, USA)	Transcutaneous vagal nerve stimulator	Acute and preventive treatment of migraine and cluster headache	Available for purchase in Australia, Brazil, Canada, Colombia, Europe, India, Malaysia, New Zealand and the UK	Cluster headache or migraine inadequately controlled with medical therapy	Acute and preventive migraine treatment	166,167
Scion Neurostim (Raleigh, North Carolina, USA)	Delivers in-ear thermoelectric caloric stimulation to the external auditory canal	Migraine prevention	Not available	A completed prospective, open-label pilot study enrolled seven participants	A sham-controlled RCT for episodic migraine prevention is ongoing	168,169
The Cefaly Arnold Kit (Cefaly Technology, Grâce-Hollogne, Belgium)	Greater occipital nerve transcutaneous electrical nerve stimulation device	Chronic migraine prevention	Available for sale in Europe	Chronic migraine patients refractory to or not tolerating standard of care	The OSCRO study for chronic migraine is ongoing	170

CGRP, calcitonin gene-related peptide; GI, gastrointestinal tract; mAb, monoclonal antibody; RCT, randomized controlled trial; SPG, sphenopalatine ganglion.

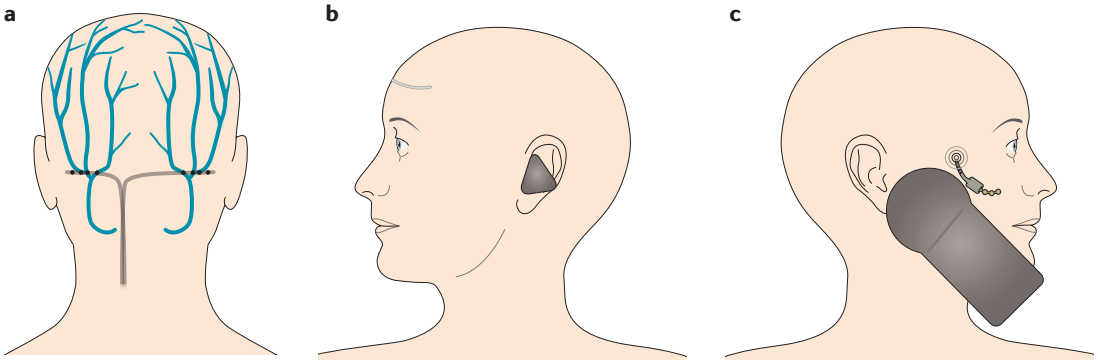

Figure 4 | **Implantable neuromodulation treatments. a** | Implantable occipital nerve stimulators are a type of peripheral nerve stimulator. The electrodes are implanted over the occipital nerves. **b** | The StimRelieve Halo Migraine System (Stimwave LLC, Fort Lauderdale, Florida, USA) is a wirelessly controlled peripheral nerve stimulator. The device uses percutaneously placed leads which are powered by a wireless external unit via radiofrequency signals rather than by an implantable pulse generator. Use of wireless technology to power the device removes the need for surgical tunnelling and creation of a pocket for battery implantation, and reduces the risk of lead migration because the leads are not attached to an implanted battery that can cause pulling. The stimulation leads can be placed over multiple pericranial peripheral nerves. **c** | The Pulsante SPG neurostimulator system (Autonomic Technologies, Inc., Redwood City, California, USA) is a multichannel peripheral nerve stimulator that is implanted transorally into the pterygopalatine fossa. It is controlled by a handheld remote control that is placed over the cheek to apply therapy. SPG, sphenopalatine ganglion.

three patients early in the trial; no cases of ulceration were reported after participants were instructed to use a customized skin cream[116].

Implantable neuromodulation devices

Implantable peripheral nerve stimulators. Implantable occipital nerve stimulators are being studied in RCTs for intractable chronic cluster headache and intractable chronic migraine (FIG. 4a). In six open-label, single-arm studies, in which a total of 59 patients with chronic cluster headache were treated with various implantable occipital nerve stimulator devices, 75% of participants experienced a >50% decrease in attack frequency, and 63% said that they would recommend implantable occipital nerve stimulators[117]. The ICON study, a double-blind, sham-controlled RCT studying implantable occipital nerve stimulators to treat medically intractable chronic cluster headache, is ongoing[118,119]. Promising results have been reported in studies of unilateral occipital nerve stimulation for hemicrania continua, and bilateral occipital nerve stimulation for medically refractory short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)[120,121].

The ONSTIM feasibility RCT investigated implantable occipital nerve stimulators for the treatment of intractable chronic migraine. The participants were randomly assigned to three groups: the preset stimulation group, the medical management group, and the adjustable stimulation group. Participants in the adjustable stimulation group were instructed to leave the stimulator switched on but could adjust the device to minimize pain. 39% of participants in the adjustable stimulation group, but only 6% in the preset stimulation group and 0% in the medical management group, had either a ≥50% reduction in the number of headache days per month or a ≥3-point reduction in average overall pain intensity[122,123]. Almost one-quarter of participants experienced lead migration.

The St. Jude Medical Genesis system (St. Jude Medical, Saint Paul, Minnesota, USA) is an implantable occipital nerve stimulator for treatment of chronic migraine. An RCT involving 157 patients did not meet its prespecified primary end point, which was a difference between active and sham groups in terms of percentage of patients experiencing a ≥50% reduction in mean daily visual analogue scale scores at 12 weeks. However, the percentage of patients experiencing a ≥30% reduction in mean daily visual analogue scores was greater in the active than in the sham group. Also, compared with sham treatment, treatment with the device resulted in significant reductions in the number of headache days (–6.0 from a baseline of 22 headache days per month versus –3.0 from a baseline of 20 headache days per month) and migraine-related disability, and direct reports provided evidence of pain relief[124]. In a 52-week open-label extension, 65% of participants in the intention-to-treat population reported that treatment with the St. Jude Medical Genesis system resulted in excellent or good headache relief. However, during the 52-week period, 40.7% of participants required surgical intervention for an adverse event, and 8.6% required hospitalization for a complication[125]. Following these results, regulatory bodies in Europe and Australia withdrew their recommendations of this device for intractable chronic migraine. In October 2014, St. Jude Medical sent a letter removing intractable chronic migraine from the product's indications for use[126]. The OPTIMISE trial is an ongoing RCT of the Precision System (Boston Scientific Corporation, Marlborough, Massachusetts, USA) for chronic migraine[127]. Two RCTs

Hemicrania continua
A primary headache disorder that results in continuous pain in one side of the face and head, with associated ipsilateral autonomic symptoms.

Lead migration
The displacement of an electrical neurostimulation lead following implantation. Lead migration is the most common complication following the surgical implantation of a peripheral nerve stimulator or spinal cord stimulator.

Sphenopalatine ganglion
The sphenopalatine ganglion, also known as the pterygopalatine ganglion, sits in the pterygopalatine fossa and contains parasympathetic nerve bodies and postsynaptic sympathetic fibres.

are also planned to investigate the StimRelieve Halo Migraine System (Stimwave LLC, Fort Lauderdale, Florida, USA) (FIG. 4b), a percutaneously placed peripheral nerve stimulator with an external pulse generator, for treatment of nonmigraine craniofacial pain[128] and chronic migraine[129] (TABLE 3).

Implantable sphenopalatine ganglion stimulator. Nerve fibres originating from or passing through the sphenopalatine ganglion (SPG) inervate end organs involved in the autonomic manifestations of migraine and the trigeminal autonomic cephalalgias, which are a family of primary headache disorders that includes cluster headache. The Pulsante SPG Neurostimulator (Autonomic Technologies, Inc., Redwood City, California, USA) is a tiny wireless, remote-controlled SPG stimulator that is currently approved in Europe for the treatment of primary headache disorders (FIG. 4c). The device is implanted via a minimally invasive, transoral approach requiring general anaesthesia.

The Pathway CH-1 study, which was conducted in Europe, assessed SPG stimulation as an acute treatment for chronic cluster headache[130]. The participants were randomly allocated to treatment with full, sub-perception or sham SPG stimulation. In total, 566 cluster attacks were treated. Among the 28 participants who completed the trial, 68% met the composite endpoint of a ≥50% decrease in pain within 15 min during attacks, a ≥50% decrease in attack frequency, or both. Full stimulation treatment was superior to both sub-perception and sham stimulation with regard to pain relief (67%, 7% and 7%, respectively)[131]. The device is the subject of ongoing trials for chronic cluster headache and migraine[132,133] (TABLE 3).

High cervical spinal cord stimulation. High cervical spinal cord stimulation is an emerging approach for the treatment of refractory chronic migraine and chronic cluster headache. The treatment works by using implantable leads to deliver electrical stimulation to the trigeminocervical complex. This intervention has been studied for both refractory chronic migraine and refractory chronic cluster headache in small single-arm, open label studies. A study of seven patients evaluated the efficacy of high cervical spinal cord stimulation for intractable chronic cluster headache[134] (FIG. 5). At the time of implantation, the participants had experienced cluster headache for a median duration of 13 years and chronic cluster headache for a median duration of 3 years. All had tried verapamil, as well as other evidence-based cluster headache preventive medications. The participants were followed up for a mean of 23 months. After implantation, attacks per day decreased from 6.0 to 1.4, attack duration decreased from 50 to 23 min, and mean attack intensity decreased from 7.4 to 4.5 on an 11-point numerical analogue scale. All participants experienced paraesthesias in the nuchal and occipital areas, and five reported paraesthesias in the trigeminal region, suggesting that stimulation of the high cervical spinal cord can provide both trigeminal and cervical neuromodulation[134]. Four of the patients were able to discontinue all preventive medications, and one further patient was able to stop triptan use[134]. However, five of the seven patients required spinal cord stimulator lead revision[135].

High cervical spinal cord stimulation has also been studied for the treatment of medically intractable chronic migraine. A retrospective cohort study was performed at a single centre in Switzerland[136]. 23 participants had

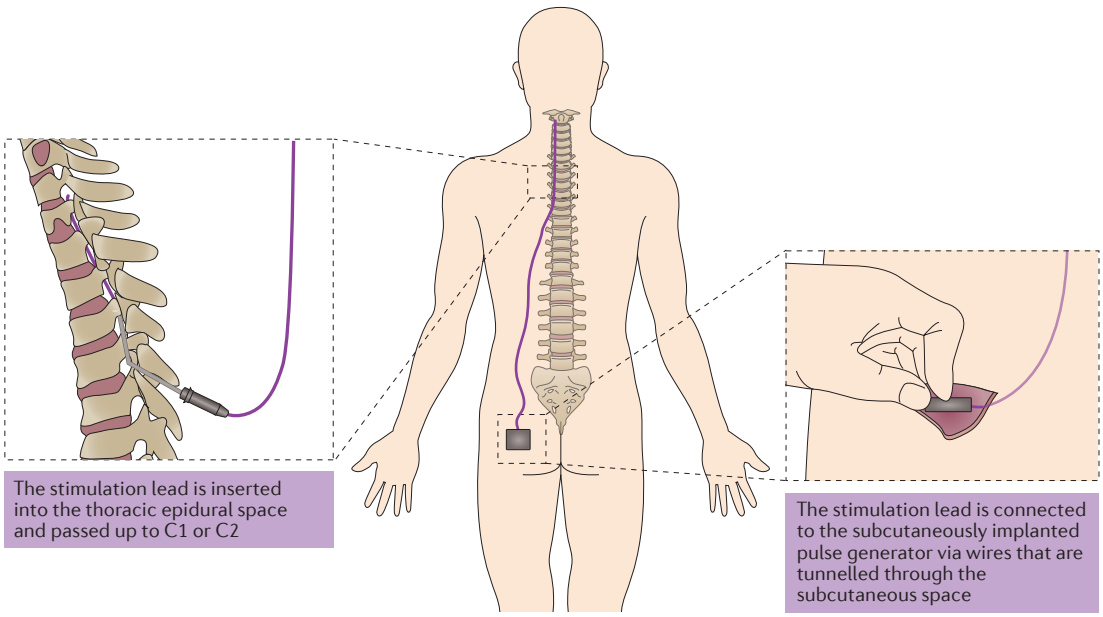

Figure 5 | **High cervical spinal cord stimulators.** High cervical spinal cord stimulation is performed by introducing a needle into the upper thoracic epidural space and advancing a wire lead through the needle superiorly until the distal tip reaches — depending on the clinical study — the C1 or C2 level. Typically, a trial implantation, during which the stimulator leads are placed and connected to an external battery, is performed first. The trial implantation is an outpatient procedure that can be performed in under an hour. If the stimulator is tolerated and effective, permanent implantation, during which the wires are tunnelled to a subcutaneous pocket where the battery is implanted, is performed at a later date.

Box 5 | **EHF criteria for refractory chronic migraine**

Refractory chronic migraine is not defined in the International Classification of Headache Disorders (ICHD)-3 beta, but the European Headache Federation (EHF) has recently proposed criteria for this condition[147]. The EHF recommends that refractory chronic migraine should be defined as ICHD-3 beta chronic migraine without medication overuse in patients who have failed to respond to treatment with at least three preventive medications at adequate dosages, each with trials of at least 3 months[148]. The proposed criteria are as follows:

A. ICHD-3 beta chronic migraine, with no medication overuse
B. Prophylactic migraine medications in adequate dosages used for at least 3 months each
C. Contraindications for or no effect of preventive medication with at least three drugs from the following classes:

- Beta blockers
  - Propranolol up to 240 mg daily
  - Metoprolol up to 200 mg daily
  - Atenolol up to 100 mg daily
  - Bisoprolol up to 10 mg daily
- Anticonvulsants
  - Valproate acid up to 1.5 g daily
  - Topiramate up to 200 mg daily
- Tricyclics
  - Amytriptyline up to 150 mg daily
- Others
  - Flunarizine up to 10 mg daily
  - Candesartan up to 16mg daily
  - OnabotulinumtoxinA 155–195 U according to the PREEMPT protocol

D. Adequate treatment of psychiatric or other comorbidities by multidisciplinary team, if available
Notes:

- Secondary headache must be excluded
- MRI indicates no underlying cause
- Laboratory and cerebrospinal fluid analyses, including cerebrospinal fluid pressure, within normal range
- Efficacy is defined as a >50% reduction in headache days
- Detoxification procedure (in or outside the hospital setting): intravenous, oral and advice-only approaches are all accepted

stimulators and impulse generators implanted, but three did not complete the questionnaire and three had infections that prompted explantation of the device. In the remaining 17 individuals who were included in the analysis, the median number of migraine days per month decreased from 28 to 9.

The Senza HF10 device (Nevro Corp., Redwood City, California, USA) is a high-frequency spinal cord stimulator that received FDA approval for chronic intractable trunk and/or extremity pain in May 2015. On the basis of efficacy data from the SEZNA-RCT trial for treatment of chronic back and leg pain, the FDA granted Nevro permission to market the Senza HF10 system as superior to conventional spinal cord stimulators[137]. Also, the Senza HF10 system's high-frequency stimulation does not produce the uncomfortable paraesthesias that are often experienced with conventional spinal cord stimulators. The system was evaluated for the treatment of medically refractory chronic migraine (BOX 5) in an investigator-initiated study of 17 individuals[138]. In this prospective, open-label study, all participants had previously received oral migraine preventive medications and onabotulinumtoxinA treatment for chronic migraine without a clinically meaningful response. All study participants were overusing acute medications at enrolment. High-frequency stimulation of the high cervical spinal cord provided a >30% reduction in headache days for eight of the patients, and six experienced a >50% reduction in headache days. An industry-initiated open-label, prospective, single-arm feasibility study is currently in the process of enrolling up to 20 individuals to study the Senza HF10 device for the treatment of refractory chronic migraine[139] (TABLE 3).

Conclusions

More-effective and better-tolerated acute and preventive treatments are needed for migraine and cluster headache patients in episodic, chronic and medically refractory subgroups. mAbs targeting CGRP or its receptor hold the most promise for preventive treatment in all of these subgroups. In phase II studies, these mAbs have shown promise in terms of both efficacy and tolerability, and the infrequent dosing regimens will avoid the hurdles to adherence that are seen with oral preventive medications. If the safety and efficacy profiles of mAbs are confirmed in phase III trials, the treatments could prove to be the most significant advance in headache treatment since the introduction of triptans. For acute treatment, the ongoing development of lasmiditan, small-molecule CGRP antagonists, and orally inhaled dihydroergotamine might expand our clinical armamentarium.

Several noninvasive neuromodulation approaches for the treatment of primary headache disorders are already available, and ongoing studies might shed light on the most appropriate indications for these interventions. Implantable neuromodulation should be reserved for patients with medically refractory headaches, in particular, medically refractory chronic cluster headache.

In the face of economic pressures to contain healthcare expenditure, clinicians and patients might encounter payer reluctance to approve coverage for new treatments as they become available. Postmarketing cost-effectiveness and comparative effectiveness studies, as well as patient and physician advocacy, might be necessary to justify payer coverage of — and help patients to have access to — the new and emerging treatments for primary headache disorders.

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Author contributions

N.M.S. and A.M.R. contributed equally to researching data for the article, discussion of the article's content, and writing and editing the manuscript before submission.

Competing interests statement

N.M.S. received an American Headache Society travel grant with funding from Avanir. A.M.R. serves on the speaker's bureaus of Avanir, Depomed and Teva, consults for Eli Lilly and serves on the advisory boards of Autonomic Technologies, Doctor Reddy's, Pernix, Teva and Zosano.