

Innovations in Headache Management – Recent Advances and Future Perspectives

Abraham J Nagy¹ and Alan M Rapoport²

1. Neurologist, Nevada Headache Institute, Las Vegas, Nevada, US; 2. Clinical Professor of Neurology,
David Geffen School of Medicine, University of California, Los Angeles, California, US

Abstract

Since the advent of triptans over two decades ago, progress on new therapeutics for headache management has seemingly slowed as few new lines of care have become available. With major advances in the understanding of headache disorder neurobiology, new therapies are on the horizon. This article will review novel delivery systems of familiar medications and new lines of care with unique therapeutic targets. Promising new therapies like calcitonin gene-related peptide (CGRP) receptor antagonists and 5-hydroxytryptamine (5-HT) 1F receptor agonists are in late-stage development. One neurotoxin has recently been approved for the prevention of chronic migraine. Neuromodulation techniques have rapidly advanced over the last few years. Several new drug targets such as nitric oxide synthase, gap junction modulators, glutamate receptor antagonists, orexin antagonists, transient receptor potential vanilloid 1 (TRPV1) receptor modulators, prostanoid receptors antagonists and pituitary adenylate cyclase 1 (PAC1) receptor antagonists await development. The therapies in the coming decade show great promise for distinctly advancing headache management.

Keywords

Calcitonin gene-related peptide antagonist, 5-hydroxytryptamine 1F receptor agonist, onabotulinumtoxinA, neuromodulation, sumatriptan, dihydroergotamine

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Correspondence: Abraham J Nagy, Nevada Headache Institute, 8285 West Arby Avenue, Suite 320, Las Vegas, NV 89113, US. E: nagyaj@nvhi.net

Migraine is a common, episodic, painful and disabling neurological disorder, with autonomic and gastrointestinal features.^{1,2} Many patients require not only acute treatment for attacks but also preventive lines of care. Evolution of headache therapies has been limited by a lack of an effective understanding of migraine pathophysiology. However, recently a number of promising targets for new drug developments have been discovered. In this review, emerging headache treatments and potential new targets for drug development will be discussed.

New Approaches with Older Therapies Variations of Triptan Therapy

Triptans currently represent the mainstay of current acute migraine therapy.³ The first triptan to become generic was sumatriptan and this has led to the design of novel delivery mechanisms.

Sumatriptan Needle-free Injection

Sumavel® DosePro®, a needle free sumatriptan injection system, came to the US market in January 2010. Delivering 6 milligram (mg) of sumatriptan subcutaneously propelled through the skin by a burst of nitrogen gas; this system is bioequivalent to the traditional needle based system when injected into the abdomen or thigh.⁴ Sumavel is an alternative for patients concerned about needles, patients with nausea and vomiting, and those not adequately managed with oral triptans.

Sumatriptan Transdermal Patches

One of the most novel approaches to delivering a medication is NP101, Zelix™, a sumatriptan iontophoretic transdermal patch. The device utilises a small electric current to drive sumatriptan across the skin delivering constant plasma levels more consistently than either oral tablet or nasal preparation, by bypassing the gastrointestinal (GI) tract.⁵ Zelix has been demonstrated to be an effective acute care medication with few of the typical triptan associated side effects.⁶ The device has been accepted for filing by the US Food and Drug Administration (FDA) and if approved, may be ideal for patients with nausea and vomiting, patients intolerant to triptan side-effects and those who do not absorb oral medications optimally due to migraine-related gastric stasis.

Intranasal Sumatriptan

Traditional nasal delivery methods suboptimally deliver sumatriptan causing much of the dose to be swallowed and absorbed slowly via the GI tract. OptiNose is a bidirectional breath-powered device that isolates the nasal cavity from the oropharynx and delivers sumatriptan powder more effectively than current technologies. Early studies of the new device have shown good efficacy and the device is currently undergoing Phase III studies.⁷

Zolmitriptan Oral Dissolvable Film

Zolmitriptan Rapidfilm® is a very thin polymeric film strip containing 2.5 and 5 mg zolmitriptan. It is designed to be swallowed with saliva

and averts the need for water. It was approved in early 2012 in Europe for acute migraine therapy and the company is currently seeking FDA approval for US distribution.

Diclofenac Potassium for Oral Solution

Cambia™ is buffered, dissolvable diclofenac potassium (50 mg) and came to market in 2010. When in solution, it has a faster time to maximum concentration (t_{max}) and onset of action than its tablet form.⁸ Cambia is the only non-steroidal anti-inflammatory drug (NSAID) approved for the acute treatment of migraine and is an excellent drug for milder migraines, especially for patients with frequent headaches.

Orally Inhaled Dihydroergotamine

Intravenous dihydroergotamine (DHE) has played a critical role in acute headache management, but is impractical for routine outpatient care. DHE administered via a nasal spray has a slow onset of action and is less effective than nasal and subcutaneous sumatriptan.⁹ Levadex® is a new oral inhaler device, which delivers DHE deep into the lung after breath actuation and onset of action is comparable to intravenous (IV) administration of DHE.¹⁰ Phase III trials demonstrated very good efficacy with acute pain relief and sustained pain freedom with low incidence of side effects, including nausea and vomiting.¹¹ Levadex should obtain FDA approval by 2013 and is a good drug selection for patients not responding to oral triptans, treating late in the migraine attack and for those with severe nausea and vomiting. As a result of the long duration of action of DHE, this medication may be advantageous for menstrual migraine.

Newer Agents

Calcitonin Gene-related Peptide Receptor Antagonists

This class of medication may be the next most promising advance in acute migraine treatment. Calcitonin gene-related peptide (CGRP), a potent vasodilator, is involved with sensory neurotransmission of meningeal trigeminovascular afferents and brain stem pain signalling, and is strongly implicated in migraine pathogenesis.¹² The first effective CGRP receptor antagonist was intravenous olcegepant (BIBN4096). It was found to be effective but further development was terminated, possibly because of low oral bioavailability.¹³ Telcagepant (MK-0974), is the first reported oral CGRP antagonist and has been found to be as equally effective as triptans for acute migraine management with fewer side effects.^{14,15} Due to liver function abnormalities when studied daily for migraine prevention, further development was terminated.¹⁶ Recently, two other CGRP antagonists, BI 44370 TA and BMS-927711, have shown promise in the management of acute migraine.^{17,18} CGRP antagonists do not have the same cardiovascular risk profile as triptans¹⁹ and if approved by the FDA, the 'gepants' class of medications will be the first non-serotonergic, non-vasoconstricting, migraine-specific line of care.

Serotonin Receptor Agonists

Triptans have a high affinity for 5-hydroxytryptamine receptor 1B (5-HT_{1B}) and 5-HT_{1D} receptors, and some are agonists at the 5-HT_{1F} receptor.²⁰ Activation of the 5-HT_{1B} accounts for the vasoconstrictive activity of triptans.²¹ Lasmiditan (COL-144), is a selective 5-HT_{1F} receptor agonist with 500-fold less affinity at 5-HT_{1B}/1D than 5-HT_{1F} receptors.²² Activation of 5-HT_{1F} receptors inhibits transmission of trigeminal nociceptive signals and is non-vasoconstrictive.²³ Phase II studies show promise as an effective acute migraine therapy and Phase III studies are under development.²⁴ If further studies

are supportive, the 'ditan' class of medications may be another non-vasoconstrictive option for acute migraine therapy.

Neurotoxin Therapy

OnabotulinumtoxinA (Botox®) recently obtained FDA approval for the management of chronic migraine. The therapeutic effect is probably unrelated to the induction of motor nerve blockade and the resultant muscle weakness, but more likely occurs through blocking glutamate, substance P and CGRP release peripherally. By inhibiting peripheral sensitisation, the drug can thereby decrease central sensitisation. Two large, double-blind, placebo-controlled, randomised, Phase III trials were able to garner FDA approval.^{25,26} Although the therapeutic gain was rather small in these studies (~10 % decrease in migraine days), two small double-blind trials found that onabotulinumtoxinA and topiramate (100–200 mg/day) had comparable efficacy for chronic migraine.^{27,28} Future studies may be needed to help further refine the role of onabotulinumtoxinA in managing chronic migraine.

Neuromodulation

Occipital Nerve Stimulation

Low frequency stimulation of the greater occipital nerve (GON) can modulate the activity of the trigeminocervical complex²⁹ as well as regions of the brain involved in the central processing of pain, like the thalamus³⁰ and the so-called pain matrix.³¹ Three randomised controlled trials have reported optimistic results in chronic migraine management with occipital nerve stimulation (ONS). One study failed to meet statistical significance;³² however, the other two demonstrated the ability to decrease headache frequency better than placebo.^{33,34} Interestingly, diagnostic occipital nerve block with steroids did not predict stimulator efficacy.³² ONS is a developing area of research and with optimised stimulation settings, it may be a useful treatment strategy, particularly for medically treatment refractory patients without medication overuse. Initial results in cluster headaches are also promising, although the number of patients treated worldwide is small. In a pooled analysis of ONS in the reported 58 subjects with cluster headache, 72 % had at least 50 % improvement.³⁵

Supraorbital Stimulation

In an open study of seven chronic migraine patients, combined occipital and supraorbital stimulation was effective and offered superior pain control compared with ONS alone.³⁶ There is a pending publication documenting a 50 % responder rate for reduction in episodic migraine with 38.1 % after supraorbital stimulation compared with 12.1 % after sham stimulation.³⁵

Vagal Nerve Stimulation

Retrospective analysis of vagal nerve stimulation for epilepsy has demonstrated some benefit for patients who also suffer from migraine.^{37,38} Two small open studies have demonstrated efficacy with both chronic migraine and cluster headache.^{39,40} Further studies are needed before wider spread adoption.

Sphenopalatine Ganglion Stimulation

The sphenopalatine ganglion (SPG), located in the pterygopalatine fossa, contains parasympathetic and sympathetic fibres directly and indirectly connecting somatic and visceral nerve structures of the face to the trigeminovascular system, the superior salivatory nucleus and the hypothalamus. Two studies investigated SPG stimulation for the acute management of cluster headache attacks and found significant benefit in attack relief.^{41,42} A wireless system using remote controlled

stimulation, the Automatic Technologies Inc. (ATI) system, was studied in a multicentre trial in Europe, obtaining good results – a manuscript regarding this system has recently been submitted. In drug resistant migraine, acute SPG stimulation was effective in five out of 10 patients.⁴³ A larger trial for migraine is now being conducted in Europe.

Deep Brain Stimulation

Neuroimaging studies performed during cluster headache attacks revealed ipsilateral activation of the hypothalamus^{44,45} and hypothalamic structural changes.⁴⁶ Stimulation near this region with an electrical lead has been studied in drug-resistant chronic cluster headache; however, the majority of these small trials were open studies without a control arm. In a pooled analysis of the reported 64 subjects who received deep brain stimulation (DBS) for cluster headaches, 70 % of subjects had at least 50 % improvement.³⁵ The largest trial has been done in Milano, Italy. This procedure is not without risk (e.g. fatal intracranial haemorrhage and transient ischaemic attack). DBS has not been explored for migraine.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive method using a weak electrical current to induce a magnetic field and modulate brain activity. Animal model experiments demonstrate TMS can inhibit cortical spreading depression (CSD) suggesting there may be an application for migraine with aura.⁴⁷

Single-pulse Transcranial Magnetic Stimulation

One study showed promising results for aborting migraine attacks⁴⁸ however, another larger study evaluating 164 patients using two TMS pulses delivered over the occipital cortex had results that were difficult to interpret.⁴⁹ Pain free responses at two, 24 and 48 hours were in favour of TMS; however, in other critical measures there was no difference between sham or sham was actually superior. Further trials are warranted to assess the usefulness of TMS for acute migraine attacks.

Repetitive Transcranial Magnetic Stimulation

It is suspected that cortical function can be inhibited by 1 hertz (Hz) stimulation and it can be excited by stimulation above 10 Hz. One study evaluated 1 Hz stimulation as a preventive for migraine and found that the frequency of migraine attacks trended towards a decrease, but this was not statistically superior to placebo.⁵⁰ Interestingly, another study found that using a high-frequency repetitive transcranial magnetic stimulation (rTMS) 20 Hz was able to suppress migraine frequency to a statically significant degree over placebo.⁵¹ Continuing to explore rTMS may be able to help clarify optimal stimulation parameters.

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is an older non-invasive application of weak currents (1–2 milliampere [mA]). It is suspected that tDCS cannot only modulate cortical excitability, but can also induce subcortical current flow.⁵² Cathode stimulation has an inhibitory effect on the cortex and the anodal stimulation has an excitatory effect.⁵³ One study, investigating the role of tDCs in migraine, applied the cathode over the visual cortex and the anode over the vertex.⁵⁴ When compared with the sham group, only headache intensity was significantly reduced, but no other endpoints were significantly improved. Another study employed a different paradigm and applied anodal stimulation to the primary motor cortex contralateral to the predominant painful side

and the cathode over the opposite supraorbital region.⁵⁵ During treatment, there was no measurable benefit; however, over the ensuing four months, there was a gradual and statistically significant decrease in pain intensity and migraine episode duration. Sample size may have been too small to detect changes during treatment. There is an ongoing Phase II study to further explore tDCS in migraine.

Emerging Therapies

Nitric Oxide Antagonism

Nitric oxide (NO) is involved with regulating vasculature diameter and has been implicated in the pathogenesis of migraine⁵⁶ by activating trigeminovascular fibres and causing release of CGRP.⁵⁷ Current interest focuses on inhibition of endothelial nitric oxide synthase (eNOS) and neuronal NOS (nNOS), two isoforms of NOS, which synthesise NO from L-arginine. Thus far, pure nNOS or eNOS inhibitors have not reached clinical trials. NXN-188, is a molecule that combines 5-HT_{1B/1D} receptor agonism with nNOS inhibition.⁵⁸ Results of a Phase II trial in acute migraine without aura failed to reach the primary endpoint (pain relief at two hours) but there was a statistically significant response for pain freedom, sustained pain freedom and use of rescue medication from four to 24 hours.⁵⁹

Gap Junction Modulators

The aura component of migraine has been attributed to CSD, a wave of electrophysiological hyperactivity in the cortex followed by a wave of inhibition.^{60,61} CSD, in part, propagates from cell to cell by utilising intercellular transmembrane conduits called gap junctions. SB-220453, tonabersat, is a gap-junction modulator and was effective in inhibiting CSD in animal models.⁶² Studies have demonstrated that in migraine attacks with frequent aura, tonabersat significantly reduced the number of aura attacks by 71 %⁶³ however, it was not effective in preventing migraine without aura.^{64,65} Tonabersat may be a potential preventive option for migraine with aura, but not for migraine without aura.

Glutamate Receptor Antagonists

Glutamate is an excitatory neurotransmitter that activates two different receptor types. Ionotropic glutamate receptors (iGluRs) are ion channel pores directly activated by glutamate. Metabotropic glutamate receptors (mGluRs) act differently and activated by glutamate, indirectly activate plasma membrane ion channels through guanine nucleotide-binding proteins (G-protein) signalling cascades. Glutamate and its receptors have multiple sites of activity in the pathophysiological cascade of migraine and play a pivotal action in nociceptive trigeminovascular pain processing.⁶⁶

Ionotropic Glutamate Receptor Antagonists

N-methyl-D-aspartate (NMDA) glutamate receptors, one type of iGluR, are activated during CSD.⁶⁷ Ketamine, a potent NMDA receptor antagonist has demonstrated some effect in aborting migraine with aura attacks in five out of 11 patients with familial hemiplegic migraine.⁶⁸ Memantine, another NMDA receptor antagonist has been able to significantly decrease migraine frequency in two studies.^{69,70} Two other iGluR types are alpha(α)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kainate receptors. Tezampanel, LY293558, a mixed AMPA/kainate receptor antagonist is non-vasoconstrictive, well tolerated, and effective in the acute treatment of migraine.⁷¹ Phase III studies for acute migraine treatment are planned. Its oral prodrug NGX426 may also be evaluated for migraine.⁷² LY466195, a GLUK5 kainate receptor antagonist, is effective

as a migraine treatment; however, its therapeutic potential may be limited because of mild reversible visual distortions.⁶⁶ Other compounds are in clinical development, including the AMPA receptor antagonist, BGG492.⁷³

Metabotropic Glutamate Receptor Antagonists

ADX10059 is a mGluR5 negative allosteric modulator. Early studies demonstrated efficacy for acute migraine; however, there were a number of side effects such as dizziness, impaired concentration and visual disturbances.⁷⁴ A large European multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study is currently assessing ADX10059 for migraine prophylaxis.

Orexin Receptor Antagonists

Orexins, peptides integral to sleep, can alter the function of key components of the trigeminovascular system associated with migraine.^{75,76} Orexin receptor antagonist, MK-6096, is a reversible antagonist of both orexin receptors, OX(1)R and OX(2)R and is currently in clinical development for insomnia.⁷⁷ A Phase I study is underway evaluating its efficacy as a migraine preventive.⁷⁸

Transient Receptor Potential Vanilloid 1 Receptor Modulators

TRPV1 is involved in the detection and regulation of body temperature as well as nociception. Located in both the central and peripheral trigeminal system, TRPV1 receptor activation leads to CGRP release.⁷⁹

Transient Receptor Potential Vanilloid 1 Agonists

Civamide is a transient receptor potential vanilloid 1 (TRPV1) agonist and calcium channel blocker that selectively depletes type-C nociceptive fiber release of excitatory neurotransmitters like CGRP and substance P. Phase II and III studies in episodic cluster headache have demonstrated the ability to significantly reduce cluster headache frequency.⁸⁰ A combined US and European Phase III study may begin soon.⁸¹ Civamide was only marginally effective for acute migraine.⁸²

Transient Receptor Potential Vanilloid 1 Antagonists

In principle TRPV1 antagonists should be effective in migraine; however, there has been little supportive evidence in chronic pain conditions.⁸³ The results of a completed Phase II trial of the TRPV1

antagonist SB-705498 for acute treatment of migraine, at the time of writing this, are not yet available.⁸⁴

Prostanoid Receptor Antagonists

Non-steroidal anti-inflammatory agents reduce headache by inhibiting cyclo-oxygenase and decreasing the production of inflammatory mediators, like prostaglandin E2 (PGE2). Animal studies have revealed that PGE2 can induce CGRP release in trigeminal neurons.⁸⁵ Elevated PGE2 levels have been demonstrated in the jugular venous blood during acute migraine attacks.⁸⁶ PGE2 can induce migraine-like headaches in healthy subjects by acting on EP2 and EP4 receptors.⁸⁷ BGC20-1531, an EP4 receptor competitive antagonist is currently undergoing a Phase II trial for migraine.

Pituitary Adenylate Cyclase-activating Peptides

Pituitary adenylate cyclase-activating peptides (PACAPs), which are released by the parasympathetic nerves, regulate cerebrovascular tone and brain haemodynamics.⁸⁸ They can induce a headache in both controls and migraineurs⁸⁹ by activating the first PAC1 receptor.⁹⁰ It is suspected that PAC1 receptor antagonists could be effective in the treatment of migraine; however, to date, no agents have thus far come to trial.

Glial Modulators

Recently, glial cells have been an intense area of focus for numerous neurological disorders. Ibudilast, originally designed several decades ago as a non-selective phosphodiesterase (PDE) inhibitor is re-emerging as AV411 and has been found to modulate glial cell activation by reducing production of pro-inflammatory cytokines, like interleukin-1 beta, tumour necrosis factor-alpha and interleukin-6, while enhancing the production of anti-inflammatory cytokine interleukin-10 and neurotrophic factors. Early studies have demonstrated efficacy in suppressing neuropathic pain and application for migraine may be upcoming.⁹¹

Conclusion

Although few new headache-based therapies have come to market over the last decade, there is a great potential for new agents because of a significantly improved understanding of migraine neurobiology. New headache-related mechanisms and validated drug targets have been identified. It seems likely that in the coming decade, the armaments to treat headache disorders will vastly expand. ■

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