

## Emerging Treatments in Headache

a report by

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Migraine is a common and disabling disease, with a one-year prevalence of 12% in Western countries such as the US.<sup>1</sup> It is associated with significant societal costs in terms of pain, bedridden days, and lost days of work. Although the development and availability of triptans over the past 17 years has revolutionized the acute treatment of migraine, many patients report an incomplete or delayed response, while others experience intolerable adverse events.<sup>2,3</sup> Furthermore, triptans are contraindicated in patients with cardiovascular disease because of their vasoconstrictive activity. Therefore, other options are needed for those who do not respond optimally to triptans, as well as for those with possible drug–drug interactions, contraindications, or risk factors. Additional goals for medications in development include rapid onset of action, bypassing the gastrointestinal (GI) tract, sustained treatment response, and solid safety and tolerability profiles. In this overview of emerging treatments in headache, the current understanding of migraine pathophysiology will be outlined and medical and surgical therapies at various stages of development will be discussed. Advances in headache diagnosis and classification will also be discussed in detail.

### Migraine Pathophysiology

In recent years, significant advances have been made in the understanding of migraine pathophysiology. Although the exact etiology remains to be defined, the currently prevailing theories are based on a hyperexcitable ‘trigeminovascular complex,’ and possibly cortex, in patients who are genetically predisposed to migraine. In these susceptible individuals, the trigeminovascular neurons release neurotransmitters, such as calcitonin gene-related peptide (CGRP) and substance P, when headache triggers are encountered. This leads to vasodilation, mast cell degranulation, increased vascular permeability, and blood vessel edema, resulting in meningeal neurogenic inflammation. This nociceptive information is transmitted from the periphery along the trigeminal nerve to the brainstem trigeminal nucleus caudalis, and then to the thalamic nuclei and the cortex, where migraine pain is ultimately perceived.<sup>4</sup> The locus coeruleus, which contains noradrenergic neurons, the dorsal raphe nuclei, which consist of serotonergic neurons, and the periaqueductal gray also play modulatory roles in the transmission of pain.<sup>5</sup>

The aura of migraine can be explained by the phenomenon of ‘cortical spreading depression’ (CSD). In experimental animals and in human neocortical and hippocampal tissue *in vitro*, CSD occurs when an electric or chemical stimulus is applied to the cerebral cortex, resulting in an excitation followed by a prolonged depolarization

of cortical neurons that gradually spreads across the cortex. This wave of depolarization occurs in conjunction with a wave of oligemia.<sup>6–10</sup> Activation of the N-methyl-D-aspartate (NMDA) receptor subtype is required to trigger CSD in the rat cerebral cortex<sup>11</sup> and in human neocortical tissues.<sup>12</sup> A similar phenomenon is hypothesized to occur spontaneously in humans, producing the aura. Recent evidence obtained from functional magnetic resonance imaging,<sup>13</sup> epidural electrophysiological recordings,<sup>14–16</sup> and intracortical multiparametric electrodes<sup>17</sup> have supported this hypothesis. The mechanism by which the headache phase develops from the aura is unknown and somewhat controversial, but it may be related to the cortical release of CGRP, nitric oxide, arachidonic acid, or various ions and their effects via the trigeminal nerve into the brainstem and back to the dural blood vessels.<sup>18,19</sup>

The rationale of the emerging therapies is based on the understanding of the above pathophysiology, with various treatments targeting different components of the operative pathways discussed above.



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## Calcitonin Gene-related Peptide Antagonists

CGRP is a neuropeptide believed to play a pivotal role in the pathophysiology of migraine, as pre-clinical and clinical findings have demonstrated a positive correlation between migraine headache and serum levels of CGRP.<sup>20</sup> CGRP is released from sensory neurons, especially activated trigeminal sensory neurons, dilates intracranial blood vessels, and may also increase nociceptive transmission centrally in the brainstem and spinal cord. After migraine pain subsides, levels return to normal. These findings led to the postulation that inhibition of either central or trigeminal CGRP release or CGRP-induced cranial

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vasodilation or mast cell degeneration might be effective in aborting migraine attacks. The development of CGRP antagonists has been of particular interest since they lack direct vasoconstrictor activity, thus offering a distinct advantage over triptans, which, although the current gold standard in acute migraine treatment, are contraindicated in patients with uncontrolled hypertension and cardiovascular, cerebrovascular, and peripheral vascular risk factors.

BIBN-4096BS (olcegepant), a non-peptide CGRP-receptor antagonist with a high affinity and specificity for the human CGRP receptor,<sup>21,22</sup> was a crucial tool in investigating the role of CGRP in migraine. Extensive animal and human studies have demonstrated that it potently inhibits the effects induced by CGRP<sup>22</sup> without affecting cerebral or systemic hemodynamics<sup>23–25</sup> when administered intravenously. It was later shown to be effective in treating migraine attacks,<sup>26</sup> with an overall response rate of 66% with the drug versus 27% with placebo. Differences from placebo were noted at 30 minutes, and the pain-free rate and rate of recurrence at two hours were favorable compared with rates after treatment with triptans.<sup>2</sup> A long duration of action was suggested by continued differences between treatment and placebo at four hours, suggesting low levels of rebound and the possibility of use as a preventive agent.<sup>27</sup> Overall, the rate of adverse events was low, and there were few typical triptan adverse events. Blood pressure, pulse rate, respiratory rate, electrocardiogram (ECG), laboratory tests, and forearm blood flow did not reveal any clinically relevant drug-induced changes. The most frequently reported adverse events were paresthesias, nausea, headache, dry mouth, and abnormal vision. A previous phase I study also reported a favorable safety and tolerability profile.<sup>28</sup>

Later, MK-0974 (telcagepant), an oral neuropeptide CGRP antagonist, was shown to be an effective treatment for moderate or severe migraine. The primary end-point was pain relief at two hours.<sup>29</sup> Similar results were obtained for the other end-points of pain freedom, improvement of associated symptoms and functional disability, and

the use of additional medication. Like BIBN-4096BS, telcagepant also demonstrated sustained pain freedom at 24 hours and was well tolerated. The most common adverse events were nausea, dizziness, and somnolence. Furthermore, telcagepant appeared to be at least comparable, if not superior, to rizatriptan on several measures, although the study was not powered to detect differences in these treatments. The results of this study will be used in future trials to determine the optimal doses for effective treatment and further characterize the clinical profile of telcagepant. The first phase III study compared different doses of telcagepant with zolmitriptan tablets, and the results were reported at the annual meeting of the American Headache Society in June in Boston. Telcagepant was equally effective as zolmitriptan with fewer adverse events. Its lack of vasoconstrictive action should make it a very useful drug, if approved.

## Transdermal Sumatriptan

Triptans are currently the gold standard for acute migraine treatment. The efficacy of these serotonin 5-HT<sub>1</sub> receptor agonists has been corroborated by extensive literature<sup>30</sup> and clinical experience.<sup>31</sup> Sumatriptan, the first triptan to be marketed worldwide, is available in oral, injectable, suppository, and nasal spray formulations, and a transdermal patch formulation (NP101) is currently under investigation. NP101 is an iontophoretic patch that uses an electrical current to propel sumatriptan across intact skin and into the underlying tissue.<sup>32</sup> A phase I study<sup>32</sup> has defined the pharmacokinetic and safety profile of this transdermal delivery system. The patches were well tolerated, with fewer adverse effects than the subcutaneous form of sumatriptan, although localized sensations and reactions at the patch site were more common than with other formulations. Results of another phase I study<sup>33</sup> comparing the pharmacokinetics of two NP101 patch formulations versus three US Food and Drug

In recent years, significant advances have been made in the understanding of migraine pathophysiology.

Administration (FDA)-approved formulations of sumatriptan (20mg nasal spray, 100mg oral tablet, and 6mg subcutaneous injection) were presented at the American Headache Society meeting in June 2008. Plasma concentrations of NP101 were more consistent and predictable compared with those of the nasal spray or tablet, probably as a result of bypassing absorption through the GI tract. Phase III double-blind, randomized, placebo-controlled studies are currently being initiated to evaluate the efficacy and safety of NP101.

## Neuromodulation

Neuromodulatory approaches have been developed for chronic headache conditions that are refractory to pharmacological therapy, such as chronic cluster headache and chronic migraine. Neuroimaging studies<sup>34–37</sup> in patients with cluster headache and other trigeminal

autonomic cephalgias (TACs) have supported the theory that activation of posterior hypothalamic neurons plays a central pathophysiological role, thus providing the rationale for deep brain (posterior hypothalamic) stimulation in the treatment of these disorders. While results have been encouraging in that most patients achieve pain reduction or cessation in spite of total failure of previous therapy, the

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procedure is invasive and carries with it a low risk for intracerebral hemorrhage.<sup>38,39</sup> As such, less invasive peripheral procedures such as occipital nerve stimulation have been proposed.

A recent systematic review<sup>40</sup> on occipital nerve stimulation in benign headache covered 10 observational studies, which included four prospective studies and several case series, case reports, and reviews. Subjects in all of the reports demonstrated improvements in pain relief, headache frequency, intensity, and duration, as well as reduced medication intake. Improvements in cluster headache patients appeared to be less dramatic, and occurred after a longer latency period than in those with occipital headaches or migraine. Although no long-term side effects were reported, short-term incidents included infection, lead displacement, and battery depletion.

The use of transcranial magnetic stimulation (TMS) for the treatment of migraine with aura is also under investigation. The administration of magnetic field pulses during the aura phase of migraine is believed to interrupt the propagation of CSD and thus abort the headache phase before it begins. A 2006 proof-of-concept study showed strong trends toward a reduction in nausea and pain at two hours in subjects who received TMS pulses. Treatment was also well tolerated.<sup>41</sup> More recently, in a randomized, double-blind, parallel-group, sham-controlled study<sup>42</sup> presented at the American Headache Society meeting in June 2008, early treatment of migraine with aura with TMS was associated with increased rates of pain freedom at two hours compared with sham treatment. Thirty-nine percent of subjects who used a portable handheld device to deliver TMS via two pulses to the occipital region during the aura of migraine were headache-free after two hours compared with 22% in the placebo group. No device-related serious adverse events were reported.

### Other Treatments in Early Stages of Development

#### *Dihydroergotamine Oral Inhaler*

MAP0004 is an orally inhaled form of dihydroergotamine (DHE) that is in phase II development. Currently, DHE is available in injectable

(intravenous, intramuscular, and subcutaneous) and nasal forms. While the intravenous form usually provides rapid relief of migraine pain, it is often given in a clinic or hospital setting and requires the supervision of a healthcare provider. Also, nausea is usually a prominent side effect. Other types of injection cause fewer adverse events but tend to work slightly more slowly. The nasal form works well in some patients but may result in inconsistent results because of poor absorption and difficulties with administration. In contrast, the inhaled form (MAP0004) can be administered at home and produces consistent dosing directly to the lung, with rapid systemic absorption and fewer adverse events in phase II trials. Compared with traditional formulations of DHE, MAP0004 delivers faster and more consistent blood levels.<sup>43</sup> Furthermore, DHE is unlikely to directly affect pulmonary function since it does not interact with receptors involved with airway regulation.<sup>44-45</sup> In a phase II trial,<sup>46</sup> it provided significant pain relief in 10 minutes, with a low incidence of recurrence at 24 hours. MAP0004 was also well tolerated, with low rates of nausea, and was even associated with decreased rates of migraine-associated nausea. Its special mechanism seems to prevent taste alteration, cough, and throat irritation. Compared with sumatriptan or rizatriptan, it may also provide more sustained relief and freedom over 24–48 hours.<sup>47</sup>

#### *Prochlorperazine Staccato Inhaler*

An orally inhaled formulation of prochlorperazine is being developed for the treatment of acute migraine. Prochlorperazine's use as an antiemetic is related to dopaminergic blockade in the chemoreceptor trigger zone. It has been used effectively intravenously in the emergency room to stop the migraine process.<sup>48-50</sup> It also has activity as an antipsychotic agent. In a phase IIB study,<sup>51</sup> staccato

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prochlorperazine met the primary efficacy end-point—headache relief at two hours post-dose—for all three doses of the study drug compared with placebo. Onset of pain relief was rapid, with all three doses showing a statistically significant pain response at 30 minutes compared with placebo. No serious adverse effects were reported. The most common drug-related side effects were taste alteration, throat irritation, cough, somnolence, breathlessness, and dizziness, all of which were dose-related.

#### *Staccato Loxapine*

Staccato loxapine is a dopamine antagonist that may be effective in the acute treatment of migraine. In a recent phase IIa multicenter, randomized, double-blind, placebo-controlled trial,<sup>52</sup> all three study doses (1.25, 2.5, and 5mg) were statistically significant compared with placebo for the primary end-point of pain relief at two hours. Using survival analysis, all doses were also statistically superior to placebo for

nausea. The treatment was well tolerated, and no serious adverse events were reported.

## Nitric Oxide Synthase Inhibitors

Nitric oxide (NO) has been hypothesized to play a role in the pathophysiology of migraine,<sup>53-55</sup> presumably via the dilation of cranial vasculature. More recently, however, evidence has suggested that the

Tonabersat (SB-220453) is a gap-junction blocker with anticonvulsant properties that is under investigation for use in the preventive treatment of migraine.

effect of NO in migraine pathogenesis may not in fact be a vascular one.<sup>56</sup> Inducible NO synthase (iNOS) has been implicated in migraine pathophysiology,<sup>57</sup> and NOS blockade has been reported to inhibit trigemino-cervical complex fos expression.<sup>58</sup> As such, NOS has been a target for migraine treatments in development.

A phase II randomized, double-blind, placebo-controlled, dose-escalating study in female patients with migraine without aura was recently conducted to assess the safety, tolerability, and efficacy of an NOS inhibitor known as MTR-106.<sup>59</sup> Significantly more subjects in the treatment group reported pain relief compared with those in the placebo group (75 versus 25%;  $p=0.025$ ). Results were also significant for the pain-free end-point (26 versus 13%), and 23% of subjects treated with MTR-106 had sustained pain freedom at 24 hours post-treatment. There were no significant changes in heart rate or blood pressure in any of the treatment groups. Out of 13 episodes of drowsiness and heart burn, 69% occurred with the highest dosage of the drug.

## Intranasal Ketorolac

The efficacy and safety of a novel intranasal formulation of ketorolac (ROX-828), a non-steroidal anti-inflammatory drug (NSAID), in the treatment of migraine and related symptoms was recently investigated in a placebo-controlled proof-of-concept study in Finland and

5-HT<sub>1F</sub> agonists may be effective in the treatment of acute migraine, without the vasoconstrictive effects associated with triptans.

Germany.<sup>60</sup> Treatment with the drug resulted in a statistically significant improvement in pain relief at most time-points over a 48-hour period compared with placebo. Statistically significant improvements in

associated migraine symptoms such as nausea and vomiting were also noted at several time-points compared with placebo, but were somewhat slow to occur. ROX-828 was generally well tolerated; the most common side effects were related to nasal irritation.

## Gap-junction Antagonists

Tonabersat (SB-220453) is a gap-junction blocker with anticonvulsant properties that is under investigation for use in the preventive treatment of migraine. It inhibits CSD and neurogenic inflammation and blocks trigeminal nerve ganglion stimulation-induced carotid vasodilatation.<sup>61,62</sup> It is currently in clinical trials, although one early study was prematurely terminated due to unexpected hypotensive episodes in four of 15 subjects.<sup>63</sup>

## AMPA Kainate Antagonists

The potential role of AMPA kainate antagonists in migraine treatment has been studied based on the implication that glutamatergic hyperactivity is involved in migraine pathophysiology. Results from a small proof-of-concept study<sup>64</sup> in which subjects were randomized to 1.2mg/kg intravenous LY293558 (an AMPA/kainate/GluR5 receptor antagonist), 6mg subcutaneous sumatriptan, or placebo showed that LY293558 produced a 69% response rate for the primary efficacy

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variable of pain relief at two hours. Fifteen percent reported adverse events compared with 53% for sumatriptan and 31% for placebo. LY293558 is now also known as tezampanel (or NGX424), and its oral prodrug, NGX 426, is also in development. A phase IIb trial on tezampanel, a parenterally administered compound, showed that a single dose of the treatment was statistically significant compared with placebo in the treatment of acute migraine headache. NGX426 is currently in phase I testing.<sup>65</sup>

## 5-HT<sub>1F</sub> Agonists

5-HT<sub>1F</sub> agonists may be effective in the treatment of acute migraine, without the vasoconstrictive effects associated with triptans. They likely act by inhibiting the activation of nociceptive neurons in the trigeminal nucleus caudalis without constricting dural blood vessels.<sup>66,67</sup> Although LY334370, a selective 5-HT<sub>1F</sub> agonist, was shown to be effective in phase II trials,<sup>68</sup> evidence of animal toxicity precluded further development of the drug.<sup>69</sup> More recently, however, a neurally acting antimigraine agent (NAAMA) that has selective 5-HT<sub>1F</sub> agonist activity, known as COL-144, showed a dose-related efficacy in the acute treatment of migraine in a phase II trial. An oral formulation of COL-144 is being developed for phase III trials, given the positive phase II trial results with the intravenous form.<sup>70</sup>

### Advances in Diagnosis

Advances in the field of headache medicine are taking place not only in the treatment realm, but also in the nosological one. The delineation of formal criteria for medical disorders is essential for both clinical and research purposes. In order to practice evidence-endorsed clinical medicine, and to perform quality research, it is mandatory to have a

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consensus on valid and reliable diagnostic criteria for the clinical entities in question. The first edition of the *International Classification of Headache Disorders* (ICHD-I) was published in 1988<sup>71</sup> by the International Headache Society (IHS) in an effort to standardize criteria for headache disorders worldwide. Although the ICHD-I represented a major advance in the understanding and classification of headache disorders, it was difficult to apply to patients with headaches of long duration (>4 hours per day) or on more days than not ('chronic daily headaches' [CDH]), and was extremely cumbersome to utilize, even for headache clinicians.<sup>72,73</sup>

In the years following the publication of the ICHD-I, numerous field trials were undertaken to validate or dispute the criteria for the different headache disorders.<sup>74-78</sup> The cumulative result of this research was an evolution in the understanding and characterization of CDH and its nomenclature as delineated in the ICHD-II, which was published in 2004. Although CDH was not included as a formal diagnosis, its subtypes were described. They included chronic migraine (CM), medication-overuse headache (MOH), chronic tension-type headache (the only CDH incorporated in the ICHD-I), new daily persistent headache (NDPH), and hemicrania continua (HC). Since then, the criteria for MOH have already been revised twice,<sup>79,80</sup> and a revision for CM was also recently published.<sup>81</sup>

Because of multiple revisions in the criteria, there exists a great deal of confusion and continuing controversy, even among prominent headache specialists, about the current official criteria for CM and MOH. The debated issue for CM involves the number of headache

days required for diagnosis. While the ICHD-II criteria required 15 days of migraine per month, this did not apply to most patients seen in clinical practice with CDH. Even episodic migraine lasting for two to three days does not necessarily meet IHS migraine criteria on each day of the attack.<sup>81</sup> As for MOH, the point of contention is whether or not a two-month withdrawal period should be required before a diagnosis can be made.

In 2006, a proposal was made to revise the criteria for both diagnoses.<sup>80</sup> For CM, the new criteria require 15 days of headache per month for at least three months, eight of which fulfill criteria for migraine or were successfully treated with acute migraine medications such as triptans or ergots. For MOH, the two-month withdrawal period before diagnosis is no longer required. Because these newest criteria have not yet been incorporated into the body of the ICHD, there is no agreement among headache specialists as to whether or not they are official. We recently proposed<sup>82</sup> that the changes outlined in 2006,<sup>80</sup> referred to as the ICHD-IIR, for the diagnosis of CM and MOH should be adopted immediately, not years from now. In addition, we need to spread the information about the new criteria and their adoption internationally so we can diagnose these common conditions more effectively and consistently.

### Conclusions

The field of headache medicine is a dynamic one, advancing rapidly and changing frequently as a result of a better understanding of both migraine pathophysiology and nosology. This in turn engenders

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higher-quality research and more targeted therapeutic approaches. For researchers and clinicians alike, the ultimate goal is to significantly reduce the frequency, duration, and intensity of migraine pain while decreasing the cost and disability associated with the disorder in the near future. With a multitude of treatment options in development, significant progress toward this end can be expected in the foreseeable future. ■

- Lipton RB, Stewart WF, Diamond S, et al., Prevalence and burden of migraine in the United States: data from the American Headache Study II, *Headache*, 2001;41:646-57.
- Ferrari MD, Roon KI, Lipton RB, Goadsby PJ, Oral triptans (serotonin 5HT<sub>1B/1D</sub> agonists) in acute migraine treatment: a meta-analysis of 53 trials, *Lancet*, 2001;358:1668-75.
- Dodick DW, Triptan nonresponder studies: implications for clinical practice, *Headache*, 2005;45:156-62.
- Moskowitz MA, The neurobiology of vascular head pain, *Ann Neurol*, 1984;16:157-68.
- Martin VT, Behbehani MM, Toward a rational understanding of migraine trigger factors, *Med Clin North Am*, 2001;85:911-41.
- Leao AAP, Spreading depression of activity in cerebral cortex, *J Neurophysiol*, 1944;7:359-90.
- Lauritzen M, Pathophysiology of the migraine aura. The spreading depression theory, *Brain*, 1994;117(Pt 1):199-210.
- Bures J, Buresova O, Drivanek J, *The mechanism and applications of Leao's spreading depression of electroencephalographic activity*, New York: Academic Press, 1974.
- Kruger H, Heinemann U, Luhmann HJ, Effects of ionotropic glutamate receptor blockage and 5-HT<sub>1A</sub> receptor activation on spreading depression in rat neocortical slices, *Neuroreport*, 1999;10:2651-6.
- Somjen GG, Mechanisms of spreading depression and hypoxic spreading depression-like depolarization, *Physiol Rev*, 2001;81:1065-96.
- Gorelova NA, Koroleva VI, Amemori T, et al., Ketamine blockade of cortical spreading depression in rats, *Electroencephalogr Clin Neurophysiol*, 1987;66:440-47.
- Gorji A, Scheller D, Straub H, et al., Spreading depression in human neocortical slices, *Brain Res*, 2001;906:74-83.
- Hadjikhani N, Sanchez Del Rio M, Wu O, et al., Mechanisms of migraine aura revealed by functional MRI in human visual cortex, *Proc Natl Acad Sci U S A*, 2001;98:4687-92.
- Strong AJ, Fabricius M, Boutelle MG, et al., Spreading and synchronous depressions of cortical activity in acutely injured human brain, *Stroke*, 2002;33:2738-43.
- Strong AJ, Detecting and characterizing spreading depression in the injured human brain, *J Cereb Blood Flow Metab*, 2003;23:748.
- Fabricius M, Fuhr S, Bhatia R, et al., Cortical spreading depression and peri-infarct depolarization in acutely injured

- human cerebral cortex, *Brain*, 2006;129:778–90.
17. Mayevsky A, Doiron A, Manor T, et al., Cortical spreading depression recorded from the human brain using a multiparametric monitoring system, *Brain Res*, 2006;740:268–74.
  18. Wahl M, Schilling L, Parsons AA, et al., Involvement of calcitonin gene-related peptide (CGRP) and nitric oxide (NO) in the pial artery dilatation elicited by cortical spreading depression, *Brain Res*, 1994;637:204–10.
  19. Bolay H, Moskowitz MA, The emerging importance of cortical spreading depression in migraine headache, *Rev Neurol*, 2005;161:655–7.
  20. Goadsby PJ, Edvinsson L, Ekman R, Vasoactive peptide release in the extracerebral circulation of humans during migraine headache, *Ann Neurol*, 1990;28:183–7.
  21. Doods H, Hallermayer G, Wu D, et al., Pharmacological profile of BIBN-4096BS. The first selective small molecular CGRP antagonist, *Br J Pharmacol*, 2000;129:420–23.
  22. Moreno MJ, Abouner R, Hebert E, et al., Efficacy of the non-peptide CGRP receptor antagonist BIBN-4096BS in blocking CGRP-induced dilations in human and bovine cerebral arteries: potential implications in acute migraine treatment, *Neuropharmacology*, 2002;42:568–76.
  23. Petersen KA, Birk S, Lassen LH, et al., The CGRP-antagonist, BIBN-4096BS, does not affect cerebral or systemic haemodynamics in healthy volunteers, *Cephalalgia*, 2005;25:139–47.
  24. Petersen KA, Lassen LH, Birk S, et al., BIBN-4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation, *Clin Pharmacol Ther*, 2005;77:202–13.
  25. Arulmani U, Schuijt MP, Heiligers JP, et al., Effects of the calcitonin gene-related peptide (CGRP) receptor antagonist BIBN4096BS on alpha-CGRP-induced regional haemodynamic changes in anaesthetised rats, *Basic Clin Pharmacol Toxicol*, 2004;94:291–7.
  26. Olesen J, Diener HC, Husstedt IW, et al., BIBN 4096 BS Clinical Proof of Concept Study Group, Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine, *N Engl J Med*, 2004;350:1104–10.
  27. Edvinsson L, Clinical data on the CGRP antagonist BIBN4096BS for treatment of migraine attacks, *CNS Drug Rev*, 2005;11:69–76.
  28. Iovino M, Feifel U, Yong C-L, et al., Safety, tolerability and pharmacokinetics of BIBN-4096BS, the first selective small molecular calcitonin gene-related peptide receptor antagonist, following single intravenous administration in health volunteers, *Cephalalgia*, 2004;24:645–56.
  29. Ho TW, Mannix LK, Fan X, et al.; On behalf of the MK-0974 Protocol 004 study group, Randomized controlled trial of an oral CGRP antagonist, MK-0974, in acute treatment of migraine, *Neurology*, 2008;70:1304–12.
  30. Ferrari MD, Goadsby PJ, Room KI, Lipton RB, Triptans (serotonin 5-HT 1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials, *Cephalalgia*, 2002;22:633–58.
  31. Lance JW, Goadsby PJ, *Mechanism and Management of Headache*, 7th ed., New York: Elsevier, 2005.
  32. Siegel SJ, O'Neill C, Dubé LM, et al., A unique iontophoretic patch for optimal transdermal delivery of sumatriptan, *Pharm Res*, 2007;24:1919–26.
  33. www.nupathe.com/pdf/16nupathe\_pr\_080630.pdf
  34. Cohen AS, Goadsby PJ, Functional neuroimaging of primary headache disorders, *Curr Neurol Neurosci Rep*, 2004;4:105–10.
  35. Sprenger T, Boecker H, Tolle TR, et al., Specific hypothalamic activation during a spontaneous cluster headache attack, *Neurology*, 2004;62:516–17.
  36. May A, Bhatta A, Buchel C, et al., Hypothalamic activation in cluster headache attacks, *Lancet*, 1998;352:275–8.
  37. May A, Bhatta A, Buchel C, et al., Functional magnetic resonance imaging in spontaneous attacks of SUNCT: short-lasting neuralgiform headache with conjunctival injection and tearing, *Ann Neurol*, 1999;46:791–4.
  38. Leone M, Deep brain stimulation in headache, *Lancet Neurol*, 2006;5:873–7.
  39. Proietti Cecchini A, Mea E, Tullio V, et al., Long-term experience of neuromodulation in TACs, *Neurol Sci*, 2008;29(Suppl. 1):S62–4.
  40. Jasper JF, Hayek SM, Implanted occipital nerve stimulators: systematic review, *Pain Physician*, 2008;11:187–200.
  41. Mohammad Y, Kothari R, Hughes G, et al., Transcranial Magnetic Stimulation (TMS) relieves migraine headache, Platform Presentation, 48th Annual Scientific Meeting of the American Headache Society, Los Angeles, June 23, 2006.
  42. Lipton RB, Dodick DW, Goadsby PJ, et al., Transcranial Magnetic Stimulation (TMS) Using a Portable Device is Effective for the Acute Treatment of Migraine with Aura: Results of a DoubleBlind, Sham Controlled, Randomized Study, Research presentation, 50th Annual Scientific Meeting of American Headache Society, Boston, June 27, 2008.
  43. Kori S, Cook R, Wang M, Shewsbury S, MAP0004, an orally inhaled formulation of DHE, delivers faster and more consistent blood levels of the drug compared to traditional oral, subcutaneous, intramuscular, and intranasal formulations of DHE, Poster, presented at the American Headache Society Annual Scientific Meeting, June 26–29, 2008.
  44. Shrewsbury SN, Kori SH, Miller SD, et al., Randomized, double-blind, placebo-controlled study of the safety, tolerability and pharmacokinetics of MAP0004 (orally-inhaled DHE) in adult asthmatics, *Curr Med Res Opin*, 2008;24:1977–85.
  45. Cook R, Shewsbury S, Pharmacological profiling of dihydroergotamine and its relevance to systemic delivery via the respiratory tract, Poster, Presented at the American Headache Society Annual Scientific Meeting, June 26–29, 2008.
  46. www.mappharma.com/Products/InhaledMigraine.htm
  47. Kori S, Shewsbury S, Newer acute migraine specific drugs may provide improved sustained relief and freedom over 24 and 48 hours post dosing, Poster, Presented at the American Headache Society Annual Scientific Meeting, June 26–29, 2008.
  48. Friedman BW, Esses D, Solorzano C, et al., A randomized controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine, *Ann Emerg Med*, 2007 (Epub ahead of print).
  49. Coppola M, Yealy DM, Leibold RA, Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache, *Ann Emerg Med*, 1995;26:541–6.
  50. Tanen DA, Miller S, French T, Riffenburgh RH, Intravenous sodium valproate versus prochlorperazine for the emergency department treatment of acute migraine headaches: a prospective, randomized, double-blind trial, *Ann Emerg Med*, 2003;41:847–53.
  51. clinicaltrials.gov/ct2/show/NCT00422812?term=Headache&rank=28
  52. Cassella J, Fishman R, Spyker D, Inhaled loxapine, a dopamine antagonist, has IV-like pharmacokinetics and reduces headache pain in patients having an acute migraine attack, Poster Presentation, European Headache and Migraine Trust International Congress, London, September 4–7, 2008.
  53. Thomsen LL, Olesen J, Nitric oxide in primary headaches, *Curr Opin Neurol*, 2001;14:315–21.
  54. Thomsen LL, Olesen J, A pivotal role of nitric oxide in migraine pain, *Ann NY Acad Sci*, 1997;835:363–72.
  55. Olesen J, Thomsen LL, Lassen LH, Olesen J, The nitric oxide hypothesis of migraine and other vascular headaches, *Cephalalgia*, 1995;15:94–100.
  56. Goadsby PJ, Migraine: emerging treatment options for preventive and acute attack therapy, *Expert Opin Emerg Drugs*, 2006;11:419–27.
  57. Reuter U, Bolay H, Jansen-Olesen I, et al., Delayed inflammation in rat meninges: implications for migraine pathophysiology, *Brain*, 2001;124:2490–2502.
  58. Hoskin KL, Bulmer DCE, Goadsby PJ, Fos expression in the trigeminocervical complex of the cat after stimulation of the superior sagittal sinus is reduced by L-NAME, *Neurosci Lett*, 1999;266:173–6.
  59. Mosek A, Groppa S, Barkan R, The efficacy and safety of MTR-106 in the treatment of acute migraine without aura in females: a randomised double-blind placebo-controlled, dose escalating study, Poster presentation, European Headache and Migraine Trust International Congress, London, September 4–7, 2008.
  60. www.medicalnewstoday.com/articles/105590.php
  61. Read SJ, Smith MI, Hunter AJ, et al., SB-220453, a potential novel antimigraine compound, inhibits nitric oxide release following induction of cortical spreading depression in the anesthetized cat, *Cephalalgia*, 1999;20:92–9.
  62. Smith MI, Read SJ, Chan WN, et al., Repeated cortical spreading depression in a gyrencephalic feline brain: inhibition by the novel benzoylamino-benzopyran SB-220453, *Cephalalgia*, 2000;20:546–53.
  63. Tyedskov JF, Iversen HK, Olesen J, A double-blind study of SB-220453 (Tonerbasat) in the glyceryltrinitrate (GTN) model of migraine, *Cephalalgia*, 2004;24:875–82.
  64. Sang CN, Ramadan NM, Wallihan RG, et al., LY293558, a novel AMPA/GluR5 antagonist, is efficacious and well-tolerated in acute migraine, *Cephalalgia*, 2004;24:596–602.
  65. www.torreypinestherapeutics.com
  66. Mitsikostas DD, del Rio MS, Moskowitz MA, Waeber C, Both 5HT1B and 5HT1F receptors modulate c-fos expression within rat trigeminal nucleus caudalis, *Eur J Pharmacol*, 1999;369:271–7.
  67. Shephard S, Edvinsson L, Cumberbatch M, et al., Possible anti-migraine mechanisms of action of the 5-HT1F receptor agonist LY334370, *Cephalalgia*, 1999;19:851–8.
  68. Goldstein DJ, Roon KI, Offen WW, et al., Selective serotonin 1F (5-HT1F) receptor agonist LY334370 for acute migraine: a randomized controlled trial, *Lancet*, 2001;358:1230–34.
  69. Ramadan NM, Buchanan TM, New and future migraine therapy, *Pharmacol Ther*, 2006;112:199–212.
  70. www.colucid.com
  71. Headache Classification Subcommittee of the International Headache Society, Classification and diagnostic criteria for headache disorders, cranial neuroalgias, and facial pain, *Cephalalgia*, 1988;8(Suppl. 7):1–96.
  72. Bigal ME, Tepper SJ, Sheftell FD, et al., Chronic daily headache: correlation between the 2004 and 1988 International Headache Society diagnostic criteria, *Headache*, 2004;44:684–91.
  73. Bigal ME, Rapoport AM, Tepper SJ, et al., The classification of chronic daily headache in adolescents – a comparison between the second edition of the International Classification of Headache Disorders and alternative diagnostic criteria, *Headache*, 2005;45:582–9.
  74. Solomon S, Lipton RB, Newman LC, Evaluation of chronic daily headache-comparison to criteria for chronic tension-type headache, *Cephalalgia*, 1992;12:365–8.
  75. Sanin LC, Mathew NT, Bellmyer LR, Ali S, The International Headache Society (IHS) headache classification as applied to a headache clinic population, *Cephalalgia*, 1994;14:443–6.
  76. Manzoni GC, Granella F, Sandrini G, et al., Classification of chronic daily headache by International Headache Society criteria: limits and new proposals, *Cephalalgia*, 1995;15:37–43.
  77. Olesen J, Rasmussen BK, The International Headache Society classification of chronic daily and near-daily headaches: a critique of the criticism, *Cephalalgia*, 1996;16:407–11.
  78. Bigal ME, Sheftell FD, Rapoport AM, et al., Chronic daily headache in a tertiary care population: correlation between the International Headache Society diagnostic criteria and proposed revisions of criteria for chronic daily headache, *Cephalalgia*, 2002;22:432–8.
  79. Silberstein SD, Olesen J, Bousser MG, et al.; on behalf of the International Headache Society, Brief report: the international classification of headache disorders, 2nd edition (ICHD-II)-revision of criteria for 8.2 Medication-overuse headache, *Cephalalgia*, 2005;25:460–65.
  80. Headache Classification Committee: Olesen J, Bousser MG, Diener HC, et al., New appendix criteria open for a broader concept of chronic migraine, *Cephalalgia*, 2006;26:742–6.
  81. Silberstein SD, Chronic migraine: diagnosis and management strategy, *Rev Neurol Dis*, 2004;1:155–60.
  82. Sun-Edelstein C, Bigal ME, Rapoport AM, Chronic migraine and medication-overuse headache: clarifying the current international headache society criteria for classification, *Cephalalgia*, 2008 (in press).