Treatment and Management of Migraine—The Road Ahead

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Abstract

The road ahead for migraine treatment depends on targeting pharmacological therapies to known pathophysiological mechananisms. Acute medications of the future may include calcitonin gene-related peptide antagonists, various glutamate antagonists, and serotonin 1F receptor agonists. New formulations of older medications include effervescent diclofenac, an orally inhaled dihydroergotamine, and sumatriptan iontophoretic patch and needless injection, all either approved in the US or in phase III trials. Preventive future treatments may include the use of botulinum neurotoxin type A for chronic daily headache and gabapentin enacarbil for episodic migraine, in addition to hormonal treatments and a potential for neuromodulators, but the preventive pipeline is far less developed. In the US, the United Council for Neurologic Subspecialty Board certification for headache medicine should raise quality of care and research in the future.

Keywords

Migraine, acute treatment, preventive treatment, future treatment, calcitonin gene-related peptide (CGRP), dihydroergotamine (DHE), sumatriptan, botulinum neurotoxin type A, gabapentin enacarbil

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Acute Treatment of Migraine

When the American Headache Society (AHS) recently celebrated its 50th anniversary, a poll was taken among the members asking them to vote on the most important achievement in the field of headache in the last 50 years. The winner was Dr Pat Humphrey and the discovery of sumatriptan.

Since sumatriptan came onto the market in 1993, first as an injectable and then as oral and nasal formulations, there has been an explosion of other migraine-specific medications in this triptan class. These include zolmitriptan, rizatriptan, naratriptan, almotriptan, frovatriptan, and eletriptan. In April 2008, the first triptan–non-steroidal anti-inflammatory drug (NSAID) combination entered the US marketplace in the form of sumatriptan–naproxen.[1] The triptan class of migraine medication has revolutionized the acute treatment of migraine for millions of migraine sufferers. It is now reasonable for most migraineurs to expect a return to full function and to be both migraine- and headache-free within two hours.

However, there remain significant gaps in the treatment of migraine, both for acute migraine and preventively. The triptans are contraindicated for anyone with coronary artery disease or peripheral vascular disease, as well as in basilar and hemiplegic migraine. In the past, rofecoxib was a good option for some of these migraineurs, and it was US Food and Drug Administration (FDA)-approved for the acute treatment of migraine before it was withdrawn from the market.

Looking ahead, there is a calcitonin gene-related peptide (CGRP) receptor antagonist, telcagepant, being developed by Merck & Co., Inc. that may be an option for those patients for whom vasoconstrictive agents are contraindicated. Significantly, telecagepant does not have the vasoconstrictive action of the triptans. Telcagepant has recently been shown to be effective in treating acute migraine pain and migraine-associated symptoms. Telcagepant appeared to be well tolerated without triptan-like side effects.[2] If FDA-approved, it could be on the market as early as 2010.

Two other acute treatment classes that show promise are the AMPA-kainate glutamate receptor antagonists, with tezampanel currently being evaluated by Torrey Pines,[3] and the serotonin 1F receptor agonists. Tezampanel had an equivocal phase II clinical trial in a subcutaneous form with an unexplained U-shaped dose–response curve,[3] while little is in the public domain about the newer serotonin 1F agonists.

Alternative delivery systems for the acute treatment of migraine are being developed and studied in clinical trials. Other oral formulations are also being studied in migraine, for example effervescent and liquid forms of diclofenac.[4] PRO-513 is a patented formulation of diclofenac potassium powder for oral solution that utilizes a unique dynamic buffering technology (DBT™) that has been demonstrated to enhance the pharmacokinetic profile of diclofenac. This formulation is expected to offer a new safe and efficacious prescription alternative for migraine patients.

Novel delivery systems for acute medications show special promise for migraine, especially for already available medications. Specifically, NuPathe Pharmaceutical has a sumatriptan iontophoretic patch delivery system that entered phase III clinical trials in January 2009 and may be on the market in early 2011. The patch employs a microprocessor that controls the pre-programmed transdermal delivery of sumatriptan over a four-hour period and represents a unique triptan treatment opportunity for migraine patients with gastrointestinal (GI) symptoms.[5] In addition, Zogenix is studying a needleless injection device for sumatriptan, the Dose-pro.[6]

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Map Pharmaceutical is in phase III clinical trials for a dihydroergotamine (DHE) orally inhaled formulation. Currently, DHE is available only as a nasal and injectable formulation.[7] Ketorolac is being tested for intranasal administration; 30mg intranasal is similar to 15–30mg intramuscularly (IM). Alexza Pharmaceuticals is studying orally inhaled neuroleptics such as prochlorperazine and loxapine for migraine treatment. These non-oral, non-injectable routes of administration could be great options for migraineurs with nausea and vomiting that prefer to avoid injections.[8]

Combination therapy for acute migraine will be important in the future treatment of migraine. More NSAID–triptan combinations in addition to sumatriptan–naproxen may emerge. In addition, combinations may include combining antinauseants with migraine-specific therapies.

Preventive Therapies

For prevention, the FDA will most likely approve Botox (botulinum neurotoxin A) for the treatment of chronic migraine (headaches and/or migraines on 15 or more days each month). Recent phase III clinical trials showed a decrease in the number of headache days in the Botox group versus placebo.[9] If approved, this option could be helpful for those headache patients who have trouble tolerating or have suboptimal improvement with the current traditional preventive medications. Importantly, no treatment is FDA-approved for chronic daily headache. Although used extensively 'off-label' for headache prevention, Botox is a cost-prohibitive option for most patients. If FDA-approved, it is hopeful there will be more insurance coverage for this relatively expensive preventive option.

Another promising preventive agent is tonabersat, a gap junction inhibitor. This drug produces dose-related inhibition of cortical spreading depression (CSD), the neuronal mechanism of aura genesis. It appears to be well-tolerated and safe in initial phase II clinical trials, although efficacy in prevention has so far been disappointing.[10]

In addition, a novel prodrug form of gabapentin, gabapentin enacarbil, is being developed for restless leg syndrome and neuropathic pain and is being studied for migraine prevention. It has a more linear bioavailability profile than gabapentin because of its uptake by nutrient transporters and so may be better tolerated in migraine prevention.[11]

Use of interventional treatments such as occipital nerve blocks, occipital nerve stimulators, other stimulators, and even microsurgery to remove a small part of the muscle pressing on the occipital nerve or in the face are being evaluated for suitability within the arsenal of treatment for headache patients; however, these treatments will be primarily for those patients visiting tertiary headache centers.[12]

We will also see clinical trials looking at the effect of hormonal therapy on migraine, especially menstrual migraine. Currently, open-label studies are ongoing indicating that continuous low-dose oral contraceptive use is associated with less headache occurrence compared with traditional cyclic use.[13] However, in the the future there will be several double-blind, placebo-controlled studies with contraceptive and hormonal products that will lead to more evidence-based medicine in the hormonal approach to female migraine patients. Such research is needed and will increase collaboration between gynecologists and the headache treatment provider.

Increasing focus on the comorbidities of the migraine patient will be part of the future of headache medicine. Looking for the underlying common pathophysiology of these shared comorbidities may lead to new specific treatment.

Guidelines and position statement papers on treating migraine patients during pregnancy and lactation are currently being written by the Women's Issues Section of the AHS. Once published, it is hoped that these position papers will help all providers who struggle with

how to treat migraine in these special populations. Given that migraine peaks in women of child-bearing years and that 50% of all pregnancies are unplanned, such guidelines and consensus expert opinion papers are needed.

The importance of biofeedback and relaxation skills will continue to be part of the treatment of migraine. More cost-effective home-based treatments will be available as validated Internet-based behavioral skills training programs become available. Such web-based approaches will make behavioral treatment of migraine more accesible to the average migraine patient.

Predictions

What other changes lie ahead in the delivery of headache medicine? I predict more and more non-neurologists will enter the field of headache medicine. Headache providers will come from the fields of internal medicine, family medicine, obstetrics and gynecology, ear, nose, and throat (ENT), oral–facial pain, pediatrics, psychiatrists, psychologists, dentists, and virtually every other field of medicine. Nurse practitioners (NPs), physician assistants (Pas), and registered nurses (RNs) will be an important part of the delivery of headache medicine, including education.

It is hoped that headache education by ancillary healthcare providers will be as common as diabetes education currently is. I envision a patient, once diagnosed with migraine headache, would then be scheduled for a migraine education consult to discuss in detail the management of his or her disease. Currently, there are headache clinics with this model of delivery, but they should be more mainstream.

The advent of the Headache Medicine Certification Exam by the United Council for Neurologic Subspecialties (UCNS) has paved the way for the recognition of headache as a specialty. Many non-neurologists have taken this exam since it was introduced in 2006; as a result, non-neurologists can now have increased recognition among colleagues and patients as having headache training and certification. For neurologists, this certification recognizes their interest and expertise in headache. This specialty certification can help differentiate between headache-passionate neurologists versus those who prefer to focus on non-headache areas in their practice such as multiple sclerosis, Parkinson's, stroke, etc. Headache certification options may extend in some form to those currently not eligible to sit the exam such as NPs, PAs, and dentists.

Increasing focus on the comorbidities of the migraine patient will be part of the future of headache medicine. Such comorbidities include depression, anxiety, bipolar disorder, fibromyalgia, irritable bowel syndrome, sleep disorders, history of abuse, and post-traumatic stress disorder, among others. Looking for the underlying common pathophysiology of these shared comorbidities may lead to new specific treatment.

What Will the Future Not Change?

The importance of getting a good history from a headache patient will never change. All of the neuroimaging currently available will never replace the importance of spending time listening to patients to obtain the history of how their headache began, a description of their headache, and all the other important information that is part of an initial headache evaluation. It is said that 'time up-front' is time well spent with a new headache patient. Spending quality time with a patient to get an accurate history, performing a hands-on exam, and providing careful follow-up and attention to comorbidites are at the very heart of headache medicine—and that will never change. ■

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1. Brandes JL, Kudrow D, Stark SR, et al., Sumatriptan-naproxen for acute treatment of migraine: a randomized trial, *JAMA*, 2007;297:1443–54.
2. Ho TW, Ferrari MD, Dodick DW, et al., Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial, *Lancet*, 2008;372:2115–23.
3. Murphy MF, Melberg SJ, Kurtz NM, Graham EA, AMPA/kainite Receptor Antagonist Tezampanel is Effective in Treating Acute Migraine, *Headache*, 2008;48:S8 (abstract).
4. Terhaag B, Hoffman A, Barkworth M, Vens-Cappell B, Bioavailability of a new effervescent tablet of diclofenac, *Int J Clin Pharmacol Ther*, 2000;38:546–51.
5. Siegel SF, O'Neill C, Dube LM, et al., A unique iontophoretic patch for optimal transdermal delivery of sumatriptan, *Pharm Res*, 2007;24:1919–26.
6. Brandes JL, Cady RK, Smith TR, et al., Usability of the Sumatriptan DosePro Needle-Free System in Adult Migraineurs during Acute Migraine Attack outside of the Clinic, *Headache*, 2008;48:S39–40 (abstract).
7. Kori SH, Shrewsbury SB, Wong M, MAP0004, an Orally Inhaled Formulation of DHE, Delivers Faster and More Consistent Therapeutic Blood Levels for the Drug Compared to Traditional Oral Subcutaneous, Intramuscular, and Intranasal Formulations of DHE, *Headache*, 2008;48:S63 (Abstract).
8. Avram M, Spyker D, Henthorn T, Cassella J, The Pharmacokinetics and Bioavailability of Prochlorperazine Delivered as a Thermally Generated Aerosol in a Single Breath to Volunteers, *Clin Pharmacol Ther*, 2009;85:71–7.
9. agn.client.shareholder.com/releasedetail.cfm?ReleaseID=333850 (accessed August 12, 2008).
10. Durham PL, Damodaram S, Thalakoti S, et al. ,Tonabersat Inhibits Trigeminal Ganglion Neuronal-Satellite Glial Cell Signaling, *Headache*, 2008;48:S5 (abstract).
11. Cundy KC, Sastry S, Luo W, et al., Clinical Pharmacokinetics of XP13512, a Novel Transporter Prodrug of Gabapentin, *J Clin Pharm Online First*, 2008 Sept 30.
12. Rogers LL and Swidan S, Stimulation of the occipital nerve for the treatment of migraine: current state and future prospects, *Acta Neurochir Suppl*, 2007;97(Pt 1):121–8.
13. Sulak P, Willis S, Kuehl T, et al., Headaches and Oral Contraceptives:Impact of Eliminating the Standard 7-Day Placebo Interval, *Headache*, 2007;47:27–37.