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Aura of Hope for Migraine Patients: Understanding the Latest Cluster of Treatment Options

Dibash Kumar Das, PhD **Steven L. Shafer, MD, FASA,** *Editor-in-Chief*

Migraine is a highly prevalent and debilitating condition affecting approximately 10%-15% of the population (*Rev Neurol* Aug 2023; *Lancet* 2012;380:2163-96). A migraine is a severe headache lasting up to 72 hours, accompanied by symptoms including nausea, vomiting, and hypersensitivity to light and sound. Women are twice as likely to experience migraine as men (*Lancet* 2012;380:2163-96).

Older theories that migraine was caused by vasodilation of meningeal arteries have been disproven by direct observation of vascular diameter using MRI (*Lancet Neurol* 2013;12:454-61). Current views classify migraine as a spectrum of diseases, ranging from acute severe headache to episodic clusters of headaches to chronic headache to "silent migraines" comprising migraine symptoms without accompanying headache (asamonitor.pub/44875me).

Research is slowly untangling the genetic, physiologic, and environmental factors responsible for the migraine spectrum of headaches. The most important observation over the past two decades is the identification of the fundamental role of calcitonin gene-related peptide (CGRP) in the onset of migraine. Two new classes of CGRP antagonists have emerged: direct antagonists (gepants) and monoclonal antibodies directed against either the CGRP protein or the CGRP receptor.

CGRP modulates cardiovascular hemostasis. As a result, migraine patients with cardiovascular disease, including Raynaud's syndrome, should be carefully monitored for adverse effects when treated with CGRP antagonists for migraine. CGRP also modulates fetoplacental vascular tone. Thus, CGRP antagonism is contraindicated in women who are pregnant. The longer-lasting CGRP monoclonal antibodies (see below) are contraindicated in women planning to conceive. The FDA package inserts warn against the use of CGRP antagonists in breastfeeding women because the safety has not been established in infants. These

Continued on page 4

Anesthesia Incident Reporting System Case 2023-10: Baby, It's Cold Outside

A 3-year-old male presented for an elective circumcision. He was an ex-32-week preemie with reactive airways and a recent URI requiring nebulized albuterol. The URI resolved 3 weeks ago, and he took a course of antibiotics. PO midazolam was given in pre-op holding area for anxiolysis, and he was calm on arrival to OR. Mask induction was performed, initially 70/30 N_2O/O_2, then sevoflurane 8%. A rotating dental resident held the face mask. I noted obstruction, instructed rotator to perform jaw thrust and a second resident to turn the APL valve to 5 cm H_2O. The $EtCO_2$ tracing went flat, I took over bag mask ventilation. I was able to give 2-3 small breaths with APL at 30 cm H_2O with FiO_2 100%, but the patient then vomited abaout 5 mL milky fluid. I instructed the resident

Continued on page 5

Advocacy: A Conversation with FAER and ASA CAO Manuel Bonilla

Roger A. Johns, MD, PhD

This isn't FAER's first time discussing the importance of advocacy in anesthesiology research. To help shed more light on this topic, it's my pleasure to share a recent conversation between ASA Chief Advocacy Officer (CAO) Manuel Bonilla, FAER President James C. Eisenach, MD, and me.

From my perspective, it is critically important for legislators to understand the breadth of what anesthesiologists do and our various roles. They need to understand how academic anesthesiology has driven the field of safety and quality in health care and provided much of the basic research behind the implementation of elements of health care science. A prime recent example is the critically important role that anesthesiology clinical care and research played in health care's response to COVID-19.

Similarly, Mr. Bonilla commented on the role anesthesiology research can play in advocacy efforts.

Continued on page 6

SPECIAL SECTION

Advocacy: Anesthesiologists Weigh In

Guest Editor: Sam L. Page, MD, FASA

23–31

PERIODICALS

In the Know: Migraine Treatments

Continued from page 1

concerns apply to the CGRP antagonists listed below and are not repeated for each new drug.

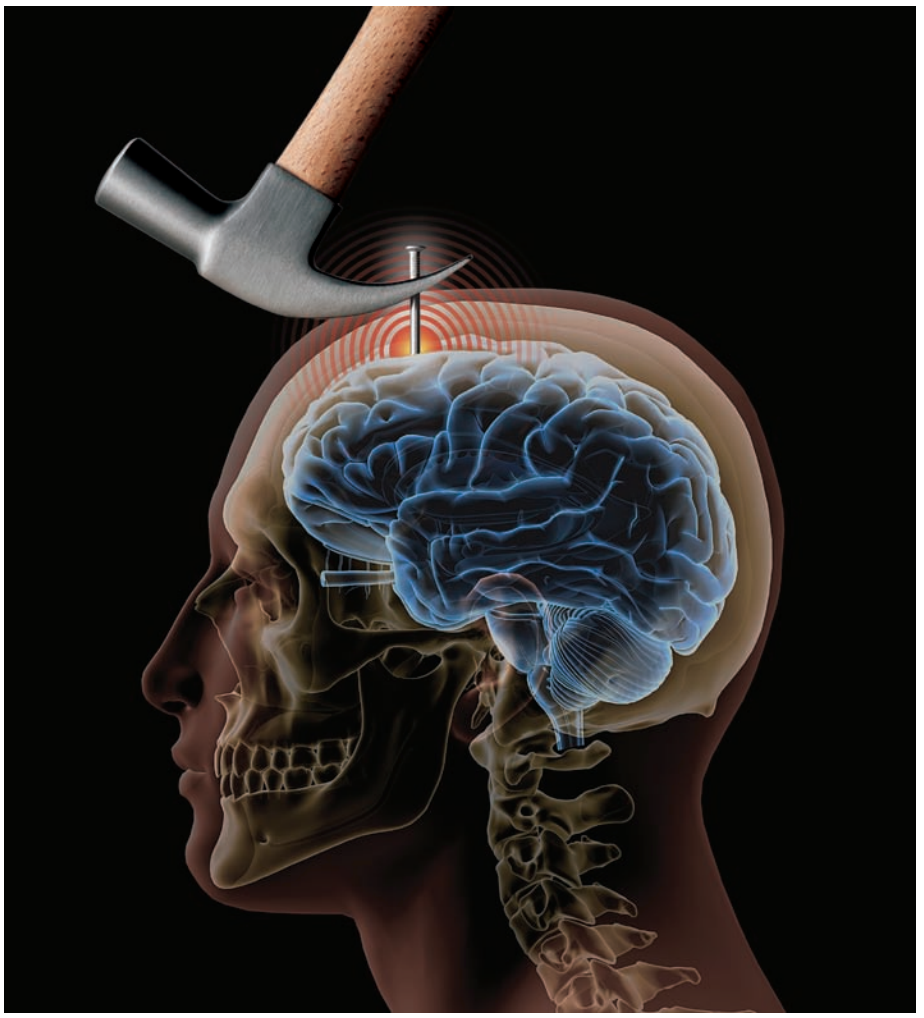
Gepants

Gepants are CGRP antagonists (*J Clin Med* 2022;11:1656). Gepants have recently been found to be effective for treatment of acute migraines and migraine prophylaxis. Unlike triptans, gepants are not associated with overuse or rebound headaches (*Drugs* 2019;28:555-67). Recently introduced gepants include the following:

- *Zavegepant* is a new nasal spray CGRP antagonist for acute migraine treatment in adults (asamonitor.pub/3OolO6u). It was approved by the FDA in July 2023. Clinical studies have shown pain relief in as little as 15 minutes after zavegepant administration. Common side effects include dizziness, dry mouth, and nausea.
- *Atogepant* is an oral CGRP antagonist approved for migraine prophylaxis in adults (asamonitor.pub/43Ot41q). It is FDA-approved for patients with debilitating migraines and poor response to other preventatives. Clinical trials have shown that atogepant reduced mean monthly migraine days and improved function compared to placebo. Factors like liver and kidney function and medication interactions should be considered before prescribing atogepant. The drug is available in three strengths.
- *Rimegepant* is a 75 mg orally disintegrating tablet CGRP antagonist used for abortive treatment of moderate to severe migraines in patients for whom triptans are contraindicated (asamonitor.pub/3E0230F). Rimegepant is also indicated for migraine prevention in prophylaxis. Common side effects include nausea, sleepiness, and dry mouth. For acute treatment, a single dose is taken. For preventive treatment, rimegepant is taken once every other day.
- *Ubrogepant* is an oral CGRP antagonist used for acute migraine treatment (asamonitor.pub/3YohQ2r). Pain relief typically occurs 30 to 60 minutes after taking the medication. The dose can be repeated if needed.

CGRP monoclonal antibodies

Monoclonal antibodies directed against either the CGRP protein or the CGRP receptor are long-lasting preventive treatments for migraines (*Neurotherapeutics* 2022;19:922-30). They are typically administered monthly or quarterly. Side effects include injection site reactions. Rarely, they are associated with an increase in blood pressure. Drug interactions are typically not a concern with monoclonal antibody therapy.



"Migraines are a common debilitating condition that impose a substantial burden on individuals and society. While a cure for migraines remains elusive, recent advancements have broadened our therapeutic options with greater efficacy and less toxicity."

- *Erenumab-aooe* is a subcutaneously injected CGRP monoclonal antibody to the CGRP receptor. It is administered as a monthly injection. The "aooe" suggests that the inventor dropped an anvil on his or her toe while naming the molecule, but we could not find any explanation for this part of the name in the literature. Fortunately, it is generally called "erenumab" today. Erenumab was the first FDA-approved monoclonal CGRP antagonist. It is indicated for episodic and chronic migraine prophylaxis, with results starting within the first week (asamonitor.pub/3s09P80). It is administered monthly via subcutaneous injections using an auto-injector.
- *Fremanezumab* is a subcutaneously injected monoclonal antibody to the CGRP protein. Fremanezumab is effective for prevention of episodic and chronic migraines (asamonitor.pub/3rVUd5c). Onset typically occurs within a week of the first injection.
- *Galcanezumab* is a subcutaneously injected monoclonal antibody to the CGRP protein. Galcanezumab is indicated for prevention of episodic and chronic migraines, as well as episodic cluster headaches (asamonitor.pub/47iG02r). Galcanezumab is administered once a month via subcutaneous injections, with the first dose consisting of two injections, followed by monthly injections. Onset can be observed within a few days.
- *Eptinezumab* is an intravenous monoclonal antibody to the CGRP protein. It is administered as an infusion every three months for prevention of episodic and chronic migraines (asamonitor.pub/3OnCivK).

Serotonin receptor agonist

Serotonin, also known as 5-hydroxytryptamine or simply 5-HT, is a well-studied neurotransmitter. The 5-HT receptor agonists, or triptans, are the current mainstays of treatment for migraine and cluster headaches (*J Pain Res* 2018;11:515-26). Lasmiditan is an agonist of the serotonin receptor. However, unlike the triptans, which are nonspecific, lasmiditan is an agonist of the 5-HT1F subtype (asamonitor.pub/47uW15y). As a result, lasmiditan acts on pain pathways without affecting blood vessels. It is considered an alternative for patients who do not tolerate triptans. Side effects include dizziness, fatigue, and tingling. Caution is advised regarding driving within eight hours due to potential dizziness.

Electrical neuromodulation

Electrical neuromodulation uses electrical stimulation to alter pain perception. Familiar forms include transcutaneous electrical neurostimulation (TENS) and spinal stimulators. Two devices have demonstrated efficacy for migraine.

- The *Nerivio® armband device* is used for the acute and preventive treatment of migraines in adults and adolescents. It attaches to the upper arm and is controlled via a smartphone app (*Pain Manag* 2022;12:267-81). Users can adjust the electrical intensity. The device includes a headache diary feature. Treatment sessions last 45 minutes, providing some pain relief. Side effects include warmth, numbness, muscle spasms, itching, tingling, and mild pain. Certain medical conditions and active implantable devices are contraindications for use.
- The *Relivion® MG headband device* is used for the acute treatment of migraines (asamonitor.pub/47uQOuH). It targets the trigeminal and occipital nerve branches using electrical signals controlled through a smartphone. Treatment lasts 20 to 40 minutes, with relief varying. Side effects include tingling, skin irritation, dizziness, and sleepiness. It is contraindicated in individuals with certain medical conditions or implants. Relivion MG provides a convenient and adjustable approach to migraine relief, but multiple sessions may be needed for optimal results.

Migraines are a common debilitating condition that impose a substantial burden on individuals and society. While a cure for migraines remains elusive, recent advancements have broadened our therapeutic options with greater efficacy and less toxicity.

As two authors who struggle with personal and family histories of migraines, we're optimistic that these developments will improve our quality of life. ■

Dibash K. Das holds a PhD in molecular, cellular, and developmental biology from CUNY Graduate Center and an advanced certificate in clinical and translational investigation from Weill Cornell Medicine.