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A RADICAL RETHINK OF MIGRAINE OFFERS HOPE TO ONE BILLION PEOPLE

Drugs that can prevent or relieve migraine attacks are only effective for some people. Research is starting to untangle the reasons why.

By Fred Schwaller

Andrea West remembers the first time she heard about a new class of migraine medication that could end her decades of pain. It was 2021 and she heard a scientist on the radio discussing the promise of gepants, a class of drug that for the first time seemed to prevent migraine attacks. West followed news about these drugs closely, and when she heard last year that atogepant was approved for use in the United Kingdom, she went straight to her physician.

West had endured migraines for 70 years. Since she started taking the drug, she hasn't had one. "It's marvellous stuff. It's genuinely changed my life," she says.

For ages, the perception of migraine has been one of suffering with little to no relief. In ancient Egypt, physicians strapped clay crocodiles to people's heads and prayed for the best. And as late as the seventeenth century, surgeons bored holes into people's skulls — some have suggested — to let the migraine out. The twentieth century brought much more effective treatments, but they did not work for a significant fraction of the roughly one billion people who

experience migraine worldwide.

Now there is a new sense of progress running through the field, brought about by developments on several fronts. Medical advances in the past few decades – including the approval of gepants and related treatments – have redefined migraine as "a treatable and manageable condition", says Diana Krause, a neuropharmacologist at the University of California, Irvine.

At the same time, research is leading to a better understanding about the condition – and pointing to directions for future work. Studies have shown, for example, that migraine is a broad phenomenon that originates in the brain and can manifest in many debilitating symptoms, including light sensitivities and aura, brain fog and fatigue. "I used to think that disability travels with pain, and it's only when the pain gets severe that people are impaired. That's not only false, but we have treatments to do something about it," says Richard Lipton, a neurologist at the Albert Einstein College of Medicine in New York City.

Researchers are trying to discover what triggers a migraine-prone brain to flip into a hyperactive state, causing a full-blown attack, or for that matter, what makes a brain prone to the condition. A new and broader approach to research and treatment is needed, says Arne May, a neurologist at the University Medical Center Hamburg–Eppendorf in Germany. To stop migraine completely and not just headache pain, he says, "we need to create new frameworks to understand how the brain activates the whole system of migraine".

Wonder drugs?

When May started researching migraine in the 1990s, the leading hypotheses were that migraine was either a psychological issue or a vascular headache disorder, with throbbing pain caused by dilation of blood vessels. The psychological associations came with stigma, May says. "No one believed people who had migraine, they just thought they didn't want to work. Nearly all of my patients at that time had to see a psychologist or psychiatrist." The field, Krause says, is still recovering from these ideas. Most clinicians have abandoned the idea that the problem is psychological, but the notion that migraine is akin to a particularly bad headache persists even now.

A lot changed in the 1990s, when May and others began conducting brain scans of people with migraine. The researchers saw for the first time that brain regions were activated during headache attacks, showing that it was more than just a vascular issue[1]. "From that point on, a lot of things changed. It was the very first time someone could point to migraine and say it's a biological disease," says May.

Researchers found that changes in the brain's activity start appearing at what's known as the premonitory phase, which begins hours to days before an attack (see 'Migraine is cyclical'). The premonitory phase is characterized by a swathe of symptoms, including nausea, food cravings, faintness, fatigue and yawning. That's often followed by a days-long migraine attack phase, which comes with overwhelming headache pain and other physical and psychological symptoms. After the attack subsides, the postdrome phase has its own associated set of symptoms that include depression, euphoria and fatigue. An interictal phase marks the time between attacks and can involve symptoms as well.

But the type, severity and causes of migraine symptoms can differ between people. Dom Horton, who is 53 and an editor in the United Kingdom, never gets headaches. But he experiences other migraine symptoms all the time. "Constant dizziness and a swimming mind are always present," he says, and they sometimes build to a severity that prevents him from leaving his house. Fiona Gartside, a 60-year-old veterinary surgeon in Scotland, experiences sensitivities to noise, light and movement, overwhelming exhaustion and headaches that get so severe that she occasionally loses consciousness, "which is a relief", she says. Migraine can even drive full-blown visual hallucinations similar to the 'reflections of the living light' painted by Hildegard von Bingen, a twelfth-century abbess who was thought to have experienced a condition that is now called migraine with aura.

Despite the variety of symptoms, it was research into normal, non-migraine associated headaches that led to revolutionary treatments for migraine. Gepant drugs and a handful of monoclonal antibodies have been designed to block activity of the calcitonin gene-related peptide (CGRP). They came from decades of research on the role of CGRP in headache and are a real "bench to bedside success story", according to Peter Goadsby, a neurologist at King's College London, who pioneered the research along with Lars Edvinsson, a neuroscientist at Lund University, Sweden, and collaborators in the 1980s.

Headache begins when sensory nerves called nociceptors in the meninges become sensitized, sending information to the brain to evoke pain. Goadsby's work showed that CGRP is a key factor in sensitizing these nociceptors. Clinical trials of drugs that block the peptide in people with migraine proved effective both in alleviating headache and sometimes in preventing attacks from starting[2]. Goadsby says it's been stunning to see the completeness of people's responses to gepants. "Patients come back and literally cry," he says. "They'd forgotten before what normal was."

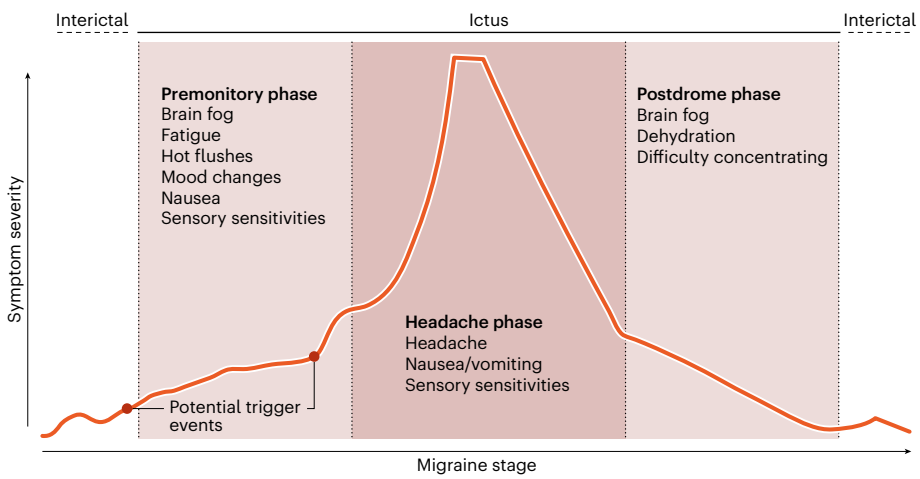
From the successes of CGRP blockers, it's tempting to view CGRP as a 'factor X' of migraine. Yet it's clear that other elements are at play. CGRP blockers work only for a subset of people, as few as one in five according to some studies[3]. And for those who do respond well to the drugs, some migraine symptoms often persist. West, for example, still has bouts of nausea even though the drug she takes, atogepant, stops her migraine attacks. And although atogepant has minimized Gartside's symptoms, migraine still dominates her life. "There is a constant juggle between prevention, medication, trigger avoidance, fatigue, fear and anticipation of attacks," she says.

Migraine in the brain

Goadsby says the mixed results of CGRP blockers show a huge gap in the biological understanding of migraine. "This tells us there are other frameworks of migraine that need to be discovered, and other pathways," he says. May agrees. He thinks the field needs a radical change in thinking to find new mechanisms of migraine. "We're focusing too much on migraine as a headache disease," he says. "The thinking for most people stops at CGRP, but

MIGRAINE IS CYCLICAL

People who are prone to migraine cycle between full-blown attack (ictus) and an interictal period between attacks. Some symptoms can occur at any time in this cycle, but they typically ramp up after triggering events that researchers are trying to understand. An attack can include a premonitory phase that lasts from hours to several days. The headache phase can last from 4 to 72 hours and is followed by a postdrome phase of up to 2 days.



SOURCE: N. KARSAN & P. J. GOADSBY *NATURE REV. NEUROL.* **14**, 699–710 (2018).

CGRP isn't the only answer." The problem, he says, is that scientists don't fully understand what a migraine attack looks like in the brain.

Studies in the past seven years or so have solidified the hypothalamus as a centre of the condition[4]. "It must involve the limbic system, of which the hypothalamus is the king," May says. The limbic system is a group of interconnected brain structures that process sensory information and regulate emotions. Studies that scanned the brains of people with migraine every few days for several weeks showed that hypothalamic connectivity to various parts of the brain increases just before a migraine attack begins, then collapses during the headache phase[5].

May and others think that the hypothalamus loses control over the limbic system about two days before the attack begins, and it results in changes to conscious experiences that might explain symptoms such as light- and sound-sensitivity, or cognitive impairments. At the same time, the breakdown of hypothalamic control puts the body's homeostatic balance out of kilter, which explains why symptoms such as fatigue, nausea, yawning and food cravings are common when a migraine is building up, says Krause.

Goadsby agrees that the hypothalamus is important, but thinks it's more complex than simply a loss of control. He hypothesizes that an attack could begin when any part of a 'migraine network', potentially including the hypothalamus, thalamus and limbic system, is overstimulated. Researchers have yet to pinpoint precisely which brain regions are part of the network, or the "exact order of batting" of when these regions are activated during an attack, Goadsby says.

Predispositions and triggers

Migraine researchers now talk of a hypothetical 'migraine threshold' in which environmental or physiological triggers tip brain activity into a dysregulated state.

The list of potential triggers is extensive. West's migraines are closely linked to certain foods and to hunger, stress and hormonal changes. She used to get terrible headaches with her period, then after menopause they developed into full-blown three-day migraines. More than half of women with migraine experience attacks every month during menstruation. And migraine is also three times more prevalent in women than in men; it's the number one debilitating issue for cisgender women in their reproductive years, and it seems equally prevalent in transgender women taking hormone replacement therapy.

Studies have shown how hormones, foods and environmental chemicals might activate signalling pathways that trigger the release of CGRP, causing headache[6]. But other triggers that some people with migraine report remain nebulous, such as weather changes.

One of the biggest questions puzzling scientists is why these events trigger migraines in some people but not others. Clearly, some answers lie in genetics, says Lyn Griffiths, a geneticist at Queensland University of Technology in Brisbane, Australia. The estimated heritability of migraine is 35–60%.

It's possible to create a polygenic risk score – an estimate of a person's likelihood of having the condition – from a survey of many genetic variants. But Griffiths says that polygenic risk scores are not reliable enough for clinicians to predict whether someone will or will not develop migraine.

Chia-Chun Chiang, a neurologist at the Mayo Clinic in Rochester, Minnesota, hopes that artificial intelligence (AI) can help to find relationships between people's biological predisposition to migraine and triggering events. She is currently training AI algorithms on large amounts of data from individuals with migraine to predict outcomes such as migraine attacks and treatment success. One algorithm, published in October last year, is 80% accurate in predicting a person's response to anti-CGRP drugs when it calculated things such as a person's body mass index, family history and the frequency and duration of their attacks[7].

"For a long period of time, people didn't take migraine seriously."

Chiang is also one of several researchers working on algorithms that can forecast migraine attacks on the basis of factors and symptoms such as sleep disturbances, weather changes, light sensitivity and nausea – data all gathered from people's diaries and wearable devices. Although still in development, Chiang expects such tools could be available in the next few years to help people know when to take precautions or treatments early. "It helps to plan their lives," she says.

A cycling disease

Progress in understanding migraine has been a turbulent affair. "For a long period of time, people didn't take migraine seriously," Chiang says. Lipton says this was exacerbated by a singular focus on headache symptoms. Even among migraine researchers, the notion that migraine consists only of a headache was so strong that funding bodies snubbed those who pursued other ideas, even as recently as the 2000s. Goadsby says that a scientist who reviewed one of his grants declared "it was a complete waste of time to study the early premonitory phase of migraine".

But things are shifting. Lipton is now co-leading a study funded by the US Food and Drug Administration that aims to develop clinical measures of migraine beyond headache. The project, called the Migraine Clinical Outcome Assessment System (MiCOAS), has characterized four new domains of migraine impairment: cognitive function; physical function; social and emotional function; and conventional migraine symptoms of headache, nausea and sensitivity to light. Lipton says measuring cognitive symptoms is particularly important to show the benefits, or lack thereof, from treatments. When some of the earliest CGRP blockers, such as erenumab and galcanezumab, were being tested in clinical trials, their success or failure was judged on headache severity, light sensitivity and nausea, but little else.

Research is starting to show that cognitive symptoms are commonly felt in between migraine attacks, as well[8]. The interictal phase was generally thought to be symptom-free, but brain imaging and electroencephalogram studies have shown that brain activity is constantly disrupted[9].

May thinks that everyone is affected by migraine-like symptoms from time to time. "We all have these same cycling systems in our brains," he says. Some people have frequent fluctuations of nausea or headache, but only some of those people experience episodic migraine attacks on top. Then a subset of people with episodic migraines develop chronic migraine – a condition characterized by 15 or more headache days per month.

For Gartside, who was diagnosed with chronic migraine in her 40s after experiencing the condition all her life, it feels like the condition has split her into two different people: "one functional and able; the other tired, emotionally labile and slow thinking." Access to a CGRP blocker in 2021 made Gartside feel whole again. "It was incredible," she says, but only for a short time: side effects made her stop the treatment 18 months later.

Migraine research has come a long way in the past five years, especially with the development of life-changing CGRP blockers. But many scientists question whether it's possible to treat all the complexities of migraine without a serious rethink that will move the field away from focusing on headache and CGRP. Until researchers "understand where migraine has its origin", says May, it will continue to dominate the lives of one billion people around the world.

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