A STUBBORN FOE

The pain, the pressure, the way it ruins your mood — everyone has experienced a headache at one time or another. But whereas most are transient and easily managed, migraines are stubborn and debilitating.

By Neil Savage; infographic by Alisdair Macdonald and Denis Mallet

1 BILLION

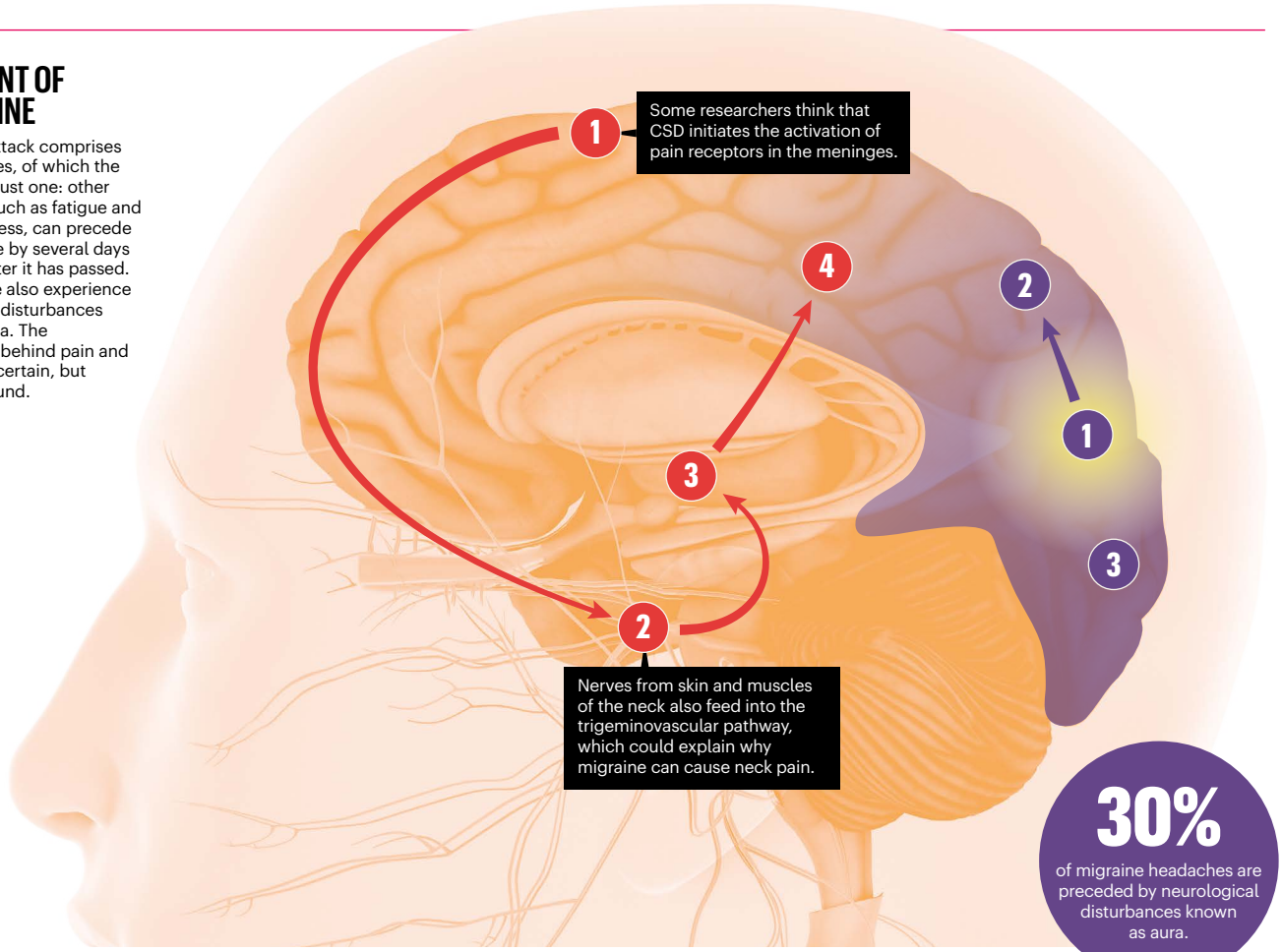
people worldwide had a diagnosis of migraine in 2016.

45.1 MILLION

years of life lived globally with disability owing to migraine in 2016.

BLUEPRINT OF A MIGRAINE

A migraine attack comprises several phases, of which the headache is just one: other symptoms, such as fatigue and muscle stiffness, can precede the headache by several days and linger after it has passed. Some people also experience neurological disturbances known as aura. The mechanisms behind pain and aura are not certain, but theories abound.



SEBASTIAN KAULITZKI/SPL/GETTY

30%

of migraine headaches are preceded by neurological disturbances known as aura.

A PAINFUL PATHWAY

The headache phase can last between 4 and 72 hours. It is characterized by pulsing or throbbing pain on one or both sides of the head, nausea and vomiting, and sensitivity to light, sound, smell and touch.

The leading theory of migraine is that headache is the result of activation of the trigeminovascular system, the network of nerves linked to blood vessels in the head.

1. Neural fibres in the meninges are stimulated to release neuropeptides, such as calcitonin gene-related peptide (CGRP). This might be because of signals from the hypothalamus.
2. Pain signals pass along the trigeminal nerve, from the meninges and large cerebral arteries to the trigeminal ganglion.
3. Signals move from the trigeminal ganglion to parts of the brain stem, thalamus, hypothalamus and basal ganglia.
4. From here, neurons carry the signals to various parts of the cortex, leading to pain and other symptoms, such as sensitivity to light and touch.

STRANGE SENSATIONS

Symptoms include seeing lights or shapes, vision loss and prickling sensations in an arm or leg. They develop over 15–20 minutes and last less than an hour.

It is widely thought that auras are caused by a slow-moving wave of depolarization that passes through the brain, known as cortical spreading depression (CSD).

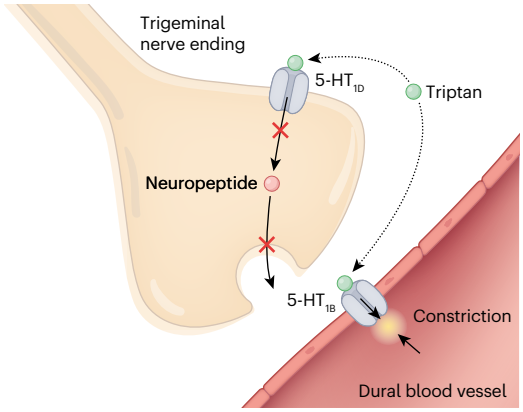
1. CSD is initiated by an accumulation of potassium ions in the space between neurons. This causes neurons to become depolarized for about 30–50 seconds.
2. The wave of depolarization spreads through the brain at around 3 millimetres per second.
3. Behind the wave, activity in the cortex is inhibited for up to 30 minutes.

PHARMACEUTICAL OPTIONS

Drugs are not the only choice for treating migraine, but there are numerous options available, including over-the-counter non-steroidal anti-inflammatory drugs, opioids and monoclonal antibodies. They work by various mechanisms, not all of which are completely understood, to interrupt the pain.

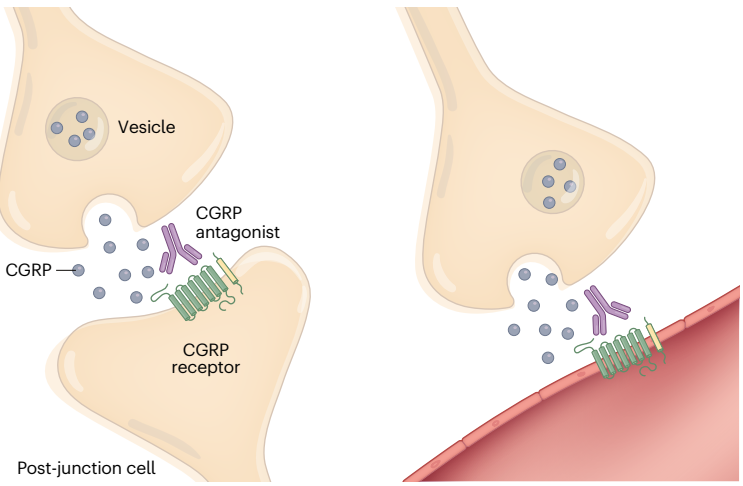
Triptans

Tryptamine-based drugs were introduced in the 1990s. They mimic the activity of the neurotransmitter serotonin (5-HT) and are effective in the early stages of an attack. At 5-HT_{1B} receptors, they reduce pain by causing cranial blood vessels to constrict. At 5-HT_{1D} receptors, they block the release of neuropeptides that trigger inflammation.



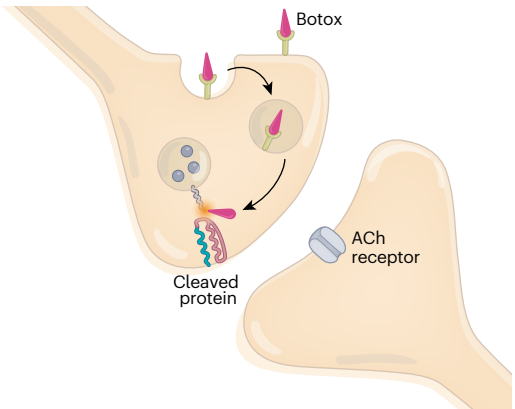
Monoclonal antibodies

Monoclonal antibodies against CGRP, first approved in 2019, are given by injection to prevent migraine attacks. The antibodies bind to either CGRP or its receptor to stop the peptide from dilating blood vessels and increasing inflammation in the meninges. They also block the transmission of pain along the trigeminal pathway.



Botox

Onabotulinumtoxin A, or Botox, is a neurotoxin that was approved for use in chronic migraine in the United States in 2010. It is given by injection and can prevent attacks for up to 90 days. Botox interferes with the neurotransmitter acetylcholine (ACh) by breaking a protein required for its release at a synapse. This prevents ACh from activating pain-receptor fibres in the brain.



MIGRAINE AND ITS COUSINS

Migraine is a major category of headache, but it is not the only type. Tension headaches are more common, yet generally less painful, whereas cluster headaches are excruciatingly painful but fortunately rare.

Migraine headaches

14% PREVALENCE

Migraines are the second most common headache, with a global age-standardized prevalence of around 14%. Often preceded by auras, migraines can cause a throbbing sensation and nausea.

- More common in women (**19%**) than in men (10%)
- Experienced on one or both sides of the head
- Pain experienced is moderate to extreme
- Attacks last from four hours to three days

Tension headaches

26% PREVALENCE

Tension headaches are the most common type of headache, with a global age-standardized prevalence of 26%. They cause a sensation of tightness or pressure, but no throbbing or nausea.

- More common in women (**31%**) than in men (21%)
- Experienced on both sides of the head
- Pain experienced is mild to moderate
- The headache usually lasts for up to a few hours

Cluster headaches

LESS THAN 1% PREVALENCE

Cluster headaches are rare, with a global age-standardized prevalence of less than 1%. People with first-hand experience describe the stabbing pain as among the worst they have ever felt.

- Two or three times more common in men than in women
- Usually experienced on one side of the head
- Pain experienced is extreme
- Attacks are typically brief, but can occur several times in one day

SOURCES: GBD 2016 Headache Collaborators. *Lancet Neurol.* **17**, 954–976 (2018); Dodick, D. W. *Headache* **58** (Suppl. 1), 4–16 (2018).