Cluster busters

Ignored by mainstream medicine, people who suffer bizarrely painful headaches are helping to test hallucinogenic drugs as a cure. Arran Frood talks to these citizen scientists.

It began the same way, every day at 3 p.m. First came the dull ache, then a sharp pain behind the right eye followed by debilitating agony. The only difference was how long it would last—anywhere from 45 minutes to three hours on a bad day.

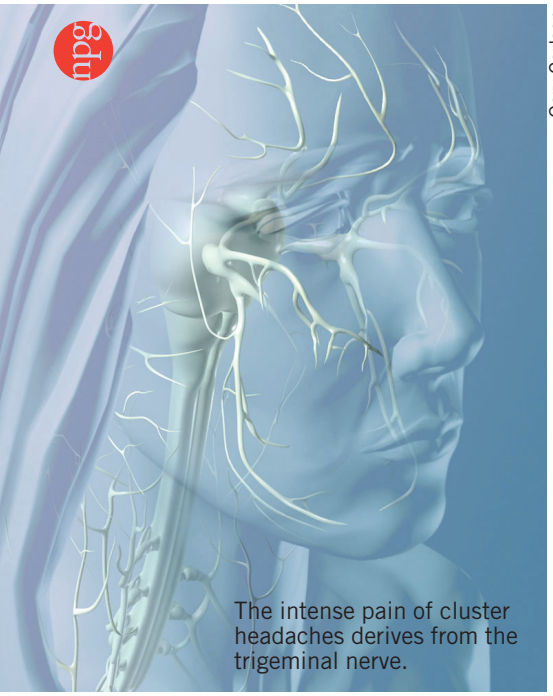
"It's a hundred times worse than the worst pain you've ever felt, but pulsating and persistent, like someone is trying to pull your eye out," says Peter May, who has suffered from cluster headaches since 1999.

The headaches are so horrible that each year people who endure them take their own lives, earning the condition the gruesome moniker of 'suicide headaches'.

"Really, you wouldn't wish it on your worst enemy," May says. "Once I was looking at a pneumatic drill… wondering if drilling into my head would relieve the pain. That's when I realized that things weren't right and I had to get it sorted somehow."

On the Internet, where many like May had begun to congregate, news had gained momentum that hallucinogenic drugs such as LSD and psilocybin, the active ingredient in 'magic' mushrooms, could provide sweet relief from the headaches.

May, a respectable middle-aged man with young children, had never even considered taking mind-expanding drugs. But after trying a veritable medicine chest of legal remedies, none of which are designed to treat cluster headaches and none of which worked, May was desperate for relief.



Gary Carlson

The intense pain of cluster headaches derives from the trigeminal nerve.

Like May, many individuals who suffer from cluster headaches have found that the illegal drugs are their only choice. Neglected by the scientific community and forced underground by the law, they have turned to the Internet to secretly find, research, promote and even sell the treatments that work.

In a classic example of 'citizen science', they have even roped in scientists to validate what their experiences have shown and plan clinical trials and other research to take the treatments forward. "I don't believe that even any of the big pharma companies would have got any further in the same period of time," says May.

Periodic pain

Often misdiagnosed as migraines, cluster headaches were noted as early as 1745 by Gerhard van Swieten, personal physician to the Austrian Empress Maria Theresa. The doctor observed that a healthy, robust man of middle age suffered from a "troublesome pain which came on every day at the same hour at the same spot above the orbit of the left eye." The man, the doctor said, "felt as if his eye was slowly forced out of its orbit with so much pain that he nearly went mad."

More than 250 years on, doctors know little more about the condition, if they have heard of it at all.

Cluster headaches are a type of neurovascular headache affecting about 1 in every 1,000 people. Their hallmark is the curious periodicity of attacks, which occur at the same time each day and in the same spot, usually in otherwise healthy middle-aged men. Only one in five sufferers is a woman.

The episodic forms of the headache, which account for about 90% of the cases, are nothing short of bizarre: one month of headaches in the spring and one in the fall is typical. This semi-annual regularity based around the equinoxes defies explanation, but at least provides some respite from the pain.

The remaining 10% of sufferers live with the chronic form and are subjected to up to eight attacks a day, each of which can last three hours if untreated or if the medication fails.

The intense pain derives from stimulation of the trigeminal nerve, which is responsible for sensation in the face. But the problem is not local to the nerve, eye or face—it lies within the brain.

Brain-imaging studies indicate the hypothalamus as the area of pathogenesis, unlike migraines where the brain stem is activated. Still, most prescribed medicines are those given for migraines, antidepressants or calcium channel blockers designed to reduce blood pressure. There are no drugs specifically for cluster headaches.

Some migraine drugs such as sumatriptan (Imigran, Imitrex) are effective when inhaled or injected, but May began to notice a worrying increase in the frequency of his daily attacks after taking sumatriptan.

The best abortive treatment isn't even a drug. Inhaling pure oxygen works for about 80% of cluster headache sufferers, although the attack must be caught within five minutes. Access to the bulky cylinder also isn't always possible.

Frustrated with the poor functionality of existing equipment, lifelong chronic sufferer Ben Khan invented the 'Clustermasx' which, Khan says, uses less oxygen, is more effective and can abort an attack in five minutes. One reviewer of his method raved that "a layer of pain is shaved off with every inhalation."

About one in five sufferers is resistant to all approved treatments, including oxygen. May, who had transitioned to chronic attacks in 2002, feared he'd soon be one of them. Then he stumbled on to a flurry of excited activity on the popular website www.clusterheadaches.com.

Magic mushrooms

Typical posts on the website raved about mushrooms of the genus *Psilocybe*, which have been used for centuries by traditional healers and shamans to commune with the spirit world.

Wary of experimenting with illegal drugs, May researched them for six months before yielding in late 2002. The results were everything he'd hoped for. "It worked immediately. I had ten pain-free days and I thought, 'I'm cured'," he says.

Through trial and error, May discovered that a small dose—too small to cause hallucinations—of the dried mushrooms taken every one or two months was enough to keep his daily attacks

Psychedelic cure: Many with cluster headaches have turned to LSD and magic mushrooms.

at bay. If a headache did force its way through, small doses of mushroom tucked under the tongue could sometimes abort an attack in just 15 minutes.

As the clusterheads collated their experiences, chronic sufferer Bob Wold set up a new site, www.clusterbusters.com, specifically to spread the message about the psychedelic drugs. "The first order of business is to let people know this life-changing treatment is out there," says Wold. "The second is to do what needs to be done to get clinical trials underway."

Anecdotal evidence is all very well, but only a few were brave enough to try the hallucinogens. Most others were sceptical, or scared of breaking the law.

One group, the evocatively named OUCH, for Organisation for the Understanding of Cluster Headaches, banned discussion of the alternative treatments from their message boards. The highly charged arguments quickly devolved into personal attacks, eventually forcing the resignations of many of the group's members.

It was clear that the community needed real scientists to give their results some credibility. Most scientists they approached baulked at the tricky legal situation. Then they found John Halpern, assistant professor of psychiatry at Harvard Medical School, who had experienced the bureaucratic quagmire of trying to work with hallucinogenic drugs.

"It's unbelievable that they came to me. It shows the power of the Internet that people with rare disorders can band together to become a more cohesive force to advocate for themselves," says Halpern, who knows of two people at his institution who have committed suicide because of cluster headaches. "I feel like we have a moral obligation to pursue this because treatment-resistant people are killing themselves," he says.

Citizen science

Halpern and his colleague Andrew Sewell began collecting the medical records of those who were using hallucinogens to relieve cluster headaches, and set up interviews and online surveys for a retrospective analysis.

Their results show that psilocybin is better at aborting acute attacks than either oxygen or sumatriptan, and LSD and psilocybin are both better at triggering and extending remission than are standard drugs (*Neurology* **66**, 1920–1922; 2006). The researchers are planning clinical trials using LSD and psilocybin.

The hallucinogens may be effective because they are similar in structure to the neurotransmitter serotonin and each affects a different suite of serotonin receptors in the brain. LSD and psilocybin, for example, both bind to the same receptors as sumatriptan, but also bind to serotonin receptors that may be involved in the circadian response to light, which suggests an effect on the biological clock to break the cluster cycle.

Although these drugs can be dangerous, there are models in place for their distribution. For instance, the infamous drug thalidomide is prescribed for treatment-resistant stomach ulcers and for leprosy, but its makers have patented a system to ensure it never reaches a pregnant woman. Xyrem, a drug prescribed for narcolepsy, contains as its active ingredient gamma-hydroxybutyrate or GHB, a date-rape drug that appeared in the 1990s.

A national registry to monitor the drugs' use and distribution could minimize the risk of misuse, Halpern says. "If we can do that for GHB and thalidomide, then I believe we can for LSD and psilocybin."

Last resort

Choosing a treatment can often come down to the best of the worst. Psychosis aside, LSD is known to affect the expression of at least seven genes. And almost nothing is known about the long-term effects in humans of ingesting psilocybin, especially in small doses.

A controversial procedure called deep-brain stimulation, used to treat Parkinson disease, is another option. In that technique, doctors implant electrodes in the hypothalamus to stimulate an area associated with the attacks. The exact mechanism of action is unknown and may be complex, but the high-frequency stimulation may inhibit or modulate the nerve cells that initiate the pain.

Massimo Leone of Milan-based Istituto Nazionale Neurologico Carlo Besta and his team have treated 19 chronic, treatment-resistant patients. "About 70% show a very good clinical response and are mainly pain free," says Leone, adding that some individuals seem to respond better to conventional medicines after the procedure.

Unfortunately, some individuals appear to become tolerant to the treatment. The technique is not without risk, either. Of six cases at a different institution, one individual died of a brain hemorrhage after the operation. "At this stage the surgery is the last resort," says Leone.

In another technique, doctors implant electrodes under the scalp to stimulate the occipital nerve, which runs from deep inside the brain to the spine, to override the pain. "Occipital nerve stimulation is going to open up a whole new chapter in treating medically intractable headache," says Peter Goadsby, an expert in cluster headaches at the Institute of Neurology, University College London.

His results, due to be published in *The Lancet*, suggest that the technique does not work for everyone but the benefits accrue over time.

Goadsby says a controlled study of hallucinogens is needed, as are follow-ups of people already using them. "Only with that data could you make a sensible comparison between intervention methods," he says.

In the meantime, the clusterheads are continuing with their attempts at citizen science. May and others began using seeds that contain lysergic acid amide, a less potent precursor to LSD, when the UK banned the sale of magic mushrooms in 2005. The seeds seem to work too, but data on correct dosage are sparse, so users are saving batches of seeds from different plant species for a rigorous chemical analysis.

May says despite the legal risks his self-medication poses, it is less scary than brain surgery, and he is determined to get the treatment validated by scientists. He also has more reason than some others to find a treatment that works—he is worried because the headaches are thought to have a genetic component.

"My biggest fear is that I might pass on the condition to my children," he says. "There's no way you could give them the alternative treatment."

Arran Frood is Nature's web editor.