New migraine therapies promise prevention

A new generation of drugs could avert migraine attacks rather than merely relieve symptoms

Philip Hunter

Migraine has been documented almost from the beginning of recorded history and was one of the first targets of pain relief therapies, though most were ineffective until the 20th century. Even today when effective drugs are available for treating attacks, there is no cure beyond the fact that in some people the condition diminishes or disappears with age. Migraine remains one of the world's most common afflictions with relatively little regional variation around a global average of 15% that is skewed three to one towards women. In the USA, the incidence of migraine or severe headache ranges from 26.1% within a 3-month period among women aged 18–44 at the top end to 4.6% among men older than 75 at the bottom [1]. According to the non-profit organization Migraine Research Foundation, this equates to 113 million lost workdays per year costing employers an estimated US\$13 billion. Around 14 million people in the USA—or 4.5% of the population—suffer from chronic and severe headaches on an almost daily basis; treatment comes in at an estimated annual cost of US\$50 billion on top of lost productivity (<http://www.migraineresearch-foundation.org/frequently-asked-questions.html>).

With this background, it is hardly surprising that migraine has been a major focus of research and clinical development. Yet, and in common with other areas of pain relief, treatment of migraine has evolved almost in the dark without a firm understanding of the condition's underlying biology. Nevertheless, after many years of work, there is now considerable optimism that the field is on the verge of substantive

progress, even though the fundamental mechanism remains elusive. “We are currently at an exciting time for migraine research and therapy with several novel therapies in the pipeline”, said Philip Holland, Head of Preclinical Research in the Headache Group at King's College, London. A new generation of drugs and non-drug therapies could prevent the headaches from appearing rather than nip attacks in the bud after the first symptoms have occurred.

Migraine is distinct from general headache because of its intensity and focus on either the front or one side of the head. It is sometimes accompanied by secondary symptoms such as nausea and acute sensitivity to light or sound, especially in severe sufferers. There are also several subtypes: the biggest distinction is between migraine with and without aura, a set of visual symptoms where sufferers see jagged flashing lights or blind spots starting just before the headache and sometimes appearing to move across the head from one side to the other. The aura usually lasts between 10 minutes and 1 hour and often finishes long before the headache.

By the early 20th century, it was clear that migraine did not respond to drugs such as paracetamol that work against other forms of headache. Clinicians turned their attention to the role of blood vessels, based on observations by many migraine sufferers of strong pulsing in the external temporal arteries accompanied by throbbing pain that was sometimes relieved by compression on that region. This idea was reinforced in the 1920s with the discovery that ergotamine

tartrate, an alkaloid that constricts blood vessels, was effective in reducing migraine pain for some sufferers [2].

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This led to the orthodoxy that migraine was caused primarily by vasodilation, which prevailed for a good 80 years. As Holland noted, the idea inspired research on ergotamines that evolved into the first drugs developed purely for migraine: the triptans. The most popular variant, sumatriptan, was approved in various countries in 1991. Sumatriptan is similar in structure to the neurotransmitter 5-hydroxytryptamine (5-HT), better known as serotonin, and acts as an agonist to the subtypes of 5-HT present in cranial arteries and veins [3]. It was assumed this was the main reason for its ability to relieve symptoms of migraine after attacks had started, but there was also evidence that it decreased the activity of the trigeminal nerve, which is responsible for pain sensation in the face and for conducting motor signals in that area, for functions such as biting. The action on that nerve was presumed to account for sumatriptan's efficacy in treating the cluster headaches sometimes triggered by migraine attacks, which cause severe pain on just one side of

the head typically focused on the eye. The injectable form of sumatriptan was highly successful, relieving cluster headaches within fifteen minutes of taking the drug in 96% of cases.

Although there was general consensus that sumatriptan operated by vasoconstriction and possibly acting on the trigeminal nerve, there was still uncertainty over its underlying mechanism of action. All that was known was that it worked and that the drug was definitely a serotonin agonist. Triptans remain very popular and still account for almost 80% of all drugs prescribed for migraine in the USA during 2009.

As Holland commented, this uncertainty triggered further research, just as triptans themselves had emerged out of earlier work on ergotamine derivatives. “Triptans have revolutionized migraine therapy and research by exploring their mechanisms of action and this has now led onto the ongoing development of non-vascular acting therapies”, he said. “We understand now that triptans change the nociceptive transmission of trigeminal input which pains killers don’t do”, said Arne May from the Institut für Systemische Neurowissenschaften Universitätsklinikum in Hamburg, Germany.

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The key point is that although triptans are indeed vasodilators, this aspect of their action is not relevant, according to Stephen Silberstein from Thomas Jefferson University in Philadelphia, USA, and former president of the American Headache Society. “Triptans work by blocking neurotransmitter release”, he said. “We know that vasoconstriction is not important because drugs that target 5HT_{1F} receptors do not have any vasoconstrictive action and appear efficacious”. The 5HT_{1F} receptors lie on the trigeminal system and are thought to block transmission of pain during migraine attacks [4]. Silberstein cited glutamate, calcitonin gene-related peptide (CGRP) and substance

P as other neurotransmitters whose release is triggered during migraine attacks.

Most research has focused on CGRP because it appears to play a central role in pain transmission during migraine attacks, activating one nerve cell and triggering its own release so that it is passed on to the next neuron in line. Its role in vasodilation has long been known [5], but it has since emerged as a primary target for preventative therapy because it has been found to circulate at higher levels in migraine sufferers even between attacks, while appearing to play a fundamental role in amplifying pain when attacks do occur [6]. There is also evidence that CGRP levels are correlated with oestrogen and the menstrual cycle, which may at least partly explain why so many more women suffer from migraine than men [6].

Calcitonin gene-related peptide is also an attractive candidate because of the potential for selectively blocking either the hormone itself or its receptors, without the vasoconstriction effect of triptans, which appears unnecessary and causes side effects in some people, such as those with cardiac conditions. “Understanding of the role of CGRP in migraine has now developed into targeted CGRP modulation”, said Holland. “At present there are at least four monoclonal antibodies targeting CGRP or the CGRP receptor going through clinical trials”. Three of these studies presented at the last meeting of the American Headache Society in June 2015 (<http://www.medscape.com/viewarticle/846893>) showed Phase 2 data indicating efficacy without discernible side effects. All three firms plan to move on to Phase III trials to compare their CGRP-based drugs with the established treatment, in this case the triptans. At least one of the firms, Amgen, is now recruiting patients for Phase III trials (<http://www.amgentrials.com/amgen/trialsummary.aspx?studyid=20120296>).

Moreover, CGRP-based drugs seem to be capable of reducing impact and severity of migraine attacks preventively. In one such trial recently completed and led by Silberstein, 264 patients were randomly given either placebo or one of two different drug regimens every 28 days for 12 weeks [7]. There was a notable placebo effect since that group experienced 37.1 fewer hours of headaches during the period but this was well exceeded by the two groups taking the drug at 59.84 hours and 67.51 hours. Such results

have been replicated by the other studies, which establishes a foundation for a new class of preventative drugs. Yet, as Silberstein pointed out, the fundamental biology underlying migraine is still unknown. New mediators and points of intervention tend to enable just better alleviation of symptoms rather than a classical cure.

There is also active research on non-drug migraine therapies with varying degrees of success, according to Teshamae Monteith, a clinical neurologist at the University of Miami Health System in Florida, USA. “The first FDA approved devices use transcutaneous nerve stimulation and transcranial magnetic stimulation”, he said. “Vagal, occipital nerve, and sphenopalatine ganglion stimulators are being investigated. Nutritional approaches with some evidence for success include riboflavin (B2), magnesium, and co-enzyme Q10 supplementation”.

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Usually, there is no rigorous scientific basis for these therapies, but there is some evidence of success in some cases. Faisal Mohammad Amin, a research fellow at the Danish Headache Centre at Glostrup Hospital, Copenhagen, commented that this lack of detail is acceptable, providing the therapy itself is safe and appears to work for at least some patients. “Anything that works on the individual patients is good”, he said. “It doesn’t need to be a specific drug. At the end of the day, we are doing all this work to help the migraineurs. If they find a way that works, we are all happy”.

Thus, nutrition, exercise and meditation can confer general health benefits in any case, but Amin is wary of surgical techniques, unless they are based on firm evidence of success, given that they are invasive and carry greater risks. Among such targeted non-drug treatments, transcranial magnetic stimulation has shown most promise and has also been approved for treatment in other countries than the USA, such as the UK (<https://www.nice.org.uk/guidance/ipg477>).

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Not all specialists in the field are convinced that non-drug therapies have shown convincing evidence beyond anecdotal cases. Jes Olesen, Professor of Neurology at the University of Copenhagen, insisted that no alternative therapy has yet stood up to full scrutiny as an effective all-round remedy. He was involved in a study refuting the long-held idea that migraine pain was accompanied by dilatation of the extracranial arteries outside the skull [8], which reinforced the argument that migraine research should focus on the peripheral and central pain pathways rather than simple arterial dilatation.

There has though been some progress identifying genetic factors implicated in migraine. “Over a dozen genes have been identified for migraine with aura and migraine without aura and many genes are associated with neuronal and vascular mechanisms”, Monteith said. These emerged from a genome-wide meta-analysis that identified loci that were correlated statistically with susceptibility to migraine [9]. However, while the analysis helps to identify individuals at risk of contracting migraine attacks, it is not, as Monteith commented, much help in developing therapies, because migraine, like other neurological conditions, is essentially polygenic. Multiple genes would have to be targeted, each one involved in multiple pathways, which would make it impossible to home in on specific factors for migraine without affecting many other neurological processes.

There is greater promise, according to Amin, in addressing one of migraine’s most

distinctive properties, namely its periodic nature. Even men who are not subject to the menstrual cycle tend to get attacks at fairly regular intervals. “Although migraine is a brain disease, it has a cyclic pattern”, Amin said. “To better understand the cyclic pattern, we need repeated measurements daily, weekly or at least monthly in order to better understand the cyclic changes over time”. This is not done at present, partly because it is more expensive to follow patients closely over time. Nevertheless, Amin suggests it would reap rewards in achieving a better understanding of the mechanisms and triggers.

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Moreover, many people who might be genetically susceptible do not get migraine, which might be due to lifestyle factors, with obesity being a major risk factor according to Monteith. To that extent, there is at least scope for non-drug therapies to prevent people developing the condition in the first place, even though their efficacy for actual sufferers remains to be proven. For those already suffering, triptans continue to be effective, while a new generation of drugs that pre-emptively target neurotransmission without causing vasoconstriction and the ensuing risks and side effects might soon become available.

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