

EDITORIAL

Cautious optimism for the future of migraine treatment

Progress on migraine research, and chronic pain research more generally, has been hampered by lack of an easily measurable biomarker. A biomarker that has sufficient sensitivity and specificity not only allows the diagnosis of disease, but also facilitates a measure of treatment response. The role of biomarkers, both radiological and biochemical, has transformed many areas of medicine for chronic disease. In neurology, for example, magnetic resonance imaging allowed the development of the McDonald criteria for multiple sclerosis,¹ and later allowed clinicians and researchers to detect not only clinical, but also radiological progression of disease, both in the form of new demyelinating lesions, and more recently in the form of volumetric loss.^{2,3}

Unfortunately, a proven biomarker is lacking in many chronic pain conditions. This absence of a physical or biochemical indicator, and the subjective nature of pain, often means that the suffering associated with chronic pain is minimised or ignored at a clinician level. Some fatalism associated with a lack of effective therapy can also enter the problem, and these individuals can often be viewed as 'heart-sink' patients. This is not peculiar to headache. Nevertheless, it is beholden on us as physicians to not only treat physical disease, but also to treat the illness and suffering of patients and address it within a biopsychosocial framework.

Migraine and headache in general are the second most common of these pain conditions (after back pain). Migraine is a condition affecting 14% of people in the world, causing significant morbidity, particularly to those of working age.⁴ It is the second most common cause of years lived with disability as calculated in the Global Burden of Disease (2019).⁵ In people aged <50 years, headache disorders are the most common cause of global disability in terms of years lived with disability.⁶ This leads to significant lost productivity, due to absenteeism.⁷ Although people with migraine may attend work despite a headache, their productivity may be sub-optimal.⁸ This lost productivity despite attendance is termed presenteeism.⁹ In 2018, Deloitte Access Economics, in conjunction with Novartis, produced a white paper to evaluate the impact of migraine in Australia.¹⁰ It estimated that approximately 4.8 million Australians were affected by migraine. The cost of migraine to the Australian society was A\$35.7 billion. Australian gross domestic product (GDP) that year was A\$1920 billion, making the relative cost 1.86% of that year's annual GDP.

Historically, and relative to other diseases, migraine has not received a level of research or clinical interest commensurate with the aforementioned burden. This may relate to the lack of presentation to general practitioners, lack of referral to tertiary neurological care, or a lack of interest and therapeutic nihilism on the part of some specialists. At present, only one headache fellowship is available to neurology trainees in Australia. While it could be argued that this reflects that care is primarily in the outpatient or private setting, the care for neuroimmunological conditions such as multiple sclerosis is similarly outpatient based, and there are at least five fellowships available in that subspecialty in comparison.

Fortunately, things may be changing and interest in headache as a subspecialty is growing, including membership of the Australia and New Zealand Headache Society. This has been spurred by the excitement surrounding the recent addition of calcitonin gene-related peptide (CGRP) inhibitors to the therapeutic armamentarium. CGRP was first identified as a putative nociceptive peptide back in 1988 by Goadsby, an Australian researcher, and his colleagues.¹¹ CGRP levels were later found to rise in spontaneous migraine¹² and exogenous CGRP could induce a migraine attack.^{13,14} CGRP is one of several nociceptive peptides isolated from the trigemino-vascular system. CGRP is expressed in both A δ and C fibre projections from the trigeminal ganglion. Both botulinum toxin and sumatriptan have been shown to block some CGRP-mediated migraine attacks. Botulinum toxin has been available for some time now for the prevention of migraine, and its mode of action is felt to be due to CGRP modulation on pain fibres that are co-localised to the nodes of Ranvier on larger somatic fibres. It suppresses CGRP levels, and also acts on glutamate, substance P and neuropeptide Y.^{15–17} The 37-amino acid CGRP binds with a G-protein coupled receptor, and is expressed throughout the nervous system, as well as peripherally in the enteric nervous system and vasculature. Development of both small peptide blockers of CGRP (the '-gepants') and monoclonal antibodies against CGRP itself or its canonical receptor have ushered in a new class of migraine therapeutics.

In this issue, Eller and Cheng describe the current state of migraine therapeutics, with a particular emphasis on the current CGRP inhibitors currently in use.¹⁸ In monoclonal antibody form, there is erenumab, fremanezumab,

galcanezumab and eptinezumab. The authors outline how and when to use specific therapies and how these therapies may improve the lives of our patients who suffer debilitating chronic migraine. Both fremanezumab and galcanezumab have been approved for use in chronic migraine under the Pharmaceutical Benefits Scheme (PBS); erenumab and eptinezumab are available on private prescription. The last is an infusion therapy and the rest subcutaneous injectables. These medications have had significant benefits for chronic migraine sufferers in Australia and worldwide.¹⁹ There remains a wide variation in response, and we are some way from a personalised migraine therapeutic regimen, since CGRP is a poor biomarker candidate, owing to low peripheral blood levels and short half-life.²⁰ On a positive note, CGRP inhibitors have been found to work quickly²¹ and a person's likely therapeutic benefit will be known within the first 3 months of use. The CGRP inhibitors seem to have a relatively minor side-effect profile, whereas other migraine prophylactic agents are often ceased due to side-effects.²² Vasoconstriction concerns were not realised, even in a coronary disease population.

As with other fields at the forefront of biotechnological innovation, these medicines come at a cost. The authors describe how and when these new medications can be used within the confines of the PBS listing. Erenumab was withdrawn from PBS application, with some indication that its evidence for cost effectiveness was insufficient. In the UK, a similar body to the PBS exists known as the National Institute for Health and Clinical Excellence (NICE). Somewhat at odds with the PBS decision, it has approved use of erenumab, fremanezumab and galcanezumab for both chronic and high frequency episodic migraine. Whether this difference relates to the two countries' different cost-benefit analyses or with their opaque price negotiations with the drug companies is a point of speculation, since presumably the efficacy data available are the same.

With migraine such a common (and underdiagnosed) problem, and particularly without an objective biomarker, the use of these therapies may grow much more

than expected. A similar issue occurred following the licensing of botulinum toxin for use in chronic migraine, where PBS forecasting underestimated the ongoing use of this therapy, resulting in a significant burden of cost on the state and therefore the taxpayer.²³ This may ultimately be behind the government strategy of cost-sharing between the available monoclonal therapies.

As doctors, we must not only be the best advocate for the patient sitting in front of us, but also for all the hypothetical patients that present in the future. We should be conscientious about how much our different treatments cost the government, since there are limitations on how much can be spent on healthcare. Not infrequently, the law of diminishing returns applies when it comes to quality-of-life improvements. We must be diligent in ensuring that the treatments we prescribe and administer to our patients are the ones that are most likely to be clinically effective as well as cost-effective. In the field of migraine, this includes simple, evidence-based lifestyle measures such as dietary, sleep and exercise advice, avoidance of smoking and excessive alcohol, as well as appropriate pharmaceutical treatment, including measures to avoid medication-overuse headache. We should retain these new medications for those who have failed more simple measures and drugs. This is not only to prevent unnecessary expenditure, but also in case of hitherto unforeseen side-effects. Despite a benign side-effect profile in clinical trials, CGRP is a ubiquitous peptide, and off-target side-effects may be revealed in the future.²⁴ Post-marketing surveillance will be important, and clinicians are encouraged to continue to follow up their patients with diligence.

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