

CLINICAL PERSPECTIVES

Migraine management: an update for the 2020s

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Migraine, CGRP monoclonal antibodies, Botox.

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[Correction added on 11th August 2022, after first online publication: Corresponding author's e-mail ID is updated.]

Received 19 October 2021; accepted 19 February 2022.

Abstract

Migraine is a common malady cutting across socioeconomic and ethnic divides in Australia. It is typically diagnosed late with significant impact on quality of life. Management options have emerged over the past several years that promise simpler treatment regimens with less potential for side-effects. The development of rationally designed migraine preventives is the most significant advance in treatment since the development of the triptans and delivers significant hope to many headache sufferers.

Introduction

Migraine is a common underdiagnosed condition that is a significant cause of disability in Australia.¹ It affects women more than men at a ratio of around 3:1.² Quality of life can be substantially affected – typically in the decades that people tend to be at their most productive.¹ Migraine can distort opportunities around career, family and social life. Economic costs borne by individuals, families and society in terms of lost productivity as well as direct and indirect health care costs are substantial.³ This malady has seen a new generation of therapeutic options introduced, providing millions of Australians renewed incentive to engage with their medical providers.⁴

Newer migraine preventives are better tolerated than medications offered in the past, with simpler regimens that are easier to manage and maintain.⁵ The real-world impression around efficacy has brightened. Forlorn patients with significant treatment fatigue should be encouraged by new options. Rationally designed, targeted therapies go some way to reduce stigma surrounding a malady that is too often attributed to stress or a failure of resilience. The emergence of efficacious, well tolerated migraine therapeutics is a prompt for health practitioners to engage with all elements of this neurological condition.

Conflict of interest: M. Eller has received speakers' fees from Allergan, Teva and Novartis. He is on the advisory board for Lundbeck and Abbvie.

This clinical perspective is heavily weighted towards a discussion of newer migraine preventives. General principles on how and when to approach the selection of acute and older preventive options will be outlined initially, followed by a more thorough discussion on onabotulinumtoxinA for chronic migraine (CM) and calcitonin gene-related peptide (CGRP) pathway monoclonal antibodies. Device therapies and non-pharmacological interventions will not be discussed. A recent review with an emphasis on migraine diagnosis and common clinical pitfalls was recently published for an Australian audience.⁶ Diagnosis is key – it is the first step before treatments can be contemplated. Patients have historically been underserved, with only one-third of patients with migraine diagnosed, and two-thirds never having been prescribed an acute medication to treat migraine such as a triptan (5HT_{1b,d} agonist).^{7,8} Building knowledge of migraine management is now, more than ever, an essential part of clinical care.

Acute therapies, diagnosis and management principles

Episodic migraine (EM) with or without aura is a diagnosis that can reflect occasional or frequent (<8) migraine days per month and likely makes up the bulk of headache sufferers that regularly present to their doctor with a complaint of head discomfort that disrupts activity.^{9,10} Most of the time all that is required for the patient to see this as a manageable problem is a diagnosis

and effective acute therapy.¹¹ When occasional headaches are very severe, leading to frequent hospital presentations, time off work or difficulty in caring for family members, a preventive should be considered.

A simple rule of thumb pertaining to acute migraine management is to trial a number of options such as non-steroidal anti-inflammatory drugs (NSAID) ± a triptan ± an antiemetic.¹² Therapeutic options within each class should be explored systematically. Medications should be used as early in an attack as possible, preferably within 30 min of onset.

NSAID should typically be tried as a first-line treatment: if ibuprofen is unhelpful, use soluble acetylsalicylic acid. If naproxen is unhelpful, try diclofenac. If one or two NSAID are reliably ineffective or poorly tolerated – they need to be tried a handful of times across different attacks – prescribe a triptan. If one triptan is unhelpful, it is worthwhile to try another. Five triptans are available in Australia. They differ in terms of the administered routes available for each product.¹³ Sumatriptan, for example, is available in oral, intranasal and subcutaneous formulations; the latter can be useful if vomiting is problematic. Naratriptan is well tolerated and relatively longer lasting, useful as a twice-daily dosing medication in or even prior to the onset of an ictus for high-risk days, such as for women prone to migraine on day –1 of their regular menstrual cycle.¹⁴ If a triptan is only partially effective, try it in combination with a NSAID. If nausea is present, consider adding in an antiemetic such as prochlorperazine or metoclopramide, domperidone and/or ondansetron.

Establishing an effective acute regimen for an individual patient is an iterative process. Efficacy and side-effects regarding triptans are often idiosyncratic, so initial lack of success should not preclude a retrial of a different medication from the same class. Most patients will ultimately alight on a regimen that is reliably efficacious with minimal side-effects if this process is followed.

Patients with frequent headaches typically do not report milder attacks. A diagnosis of CM is often missed as a result (Box 1). Asking patients to report how many days a week where they are completely without head discomfort is a good place to start. CM likely affects approximately 3% of the Australian population and is estimated to affect 7.6% of Australian migraine sufferers.^{15,16} In this group, acute migraine medications are more likely to be overused with potential to develop medication overuse headaches.¹⁷ An effective, well tolerated preventive strategy is integral in management of this cohort.

Preventive therapies

Oral medications

Several medications have been used in clinical care as migraine preventives for decades. These drugs were not

Box 1 ICHD diagnostic criteria for chronic migraine¹⁰

- A** Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months and fulfilling criteria B and C.
- B** Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*.
- C** On ≥8 days/month for >3 months fulfilling any of the following:
 - 1** criteria C and D for 1.1 *Migraine without aura*
 - 2** criteria B and C for 1.2 *Migraine with aura*
 - 3** criteria A and B for 1.5 *Probable migraine*
- D** Not better accounted for by another ICHD-3 diagnosis.

specifically developed to treat migraine. While they are often well tolerated and efficacious in individuals, many patients do not persist with prescribed medications due to any combination of side-effects, lack of efficacy and/or lack of understanding of what to expect and how to use them.⁵ Medications typically need to be titrated and used at the target dose for at least 6–8 weeks to have an adequate sense of efficacy. Efficacy can be measured by a reduction in monthly migraine days from baseline and decrement in migraine intensity; attacks typically become more responsive to acute treatment, which is required less often. A 30–50% reduction in either frequency or intensity seems to correlate with reduction in disability in the real-world setting.¹⁸

Access to newer therapies for migraine require an adequate trial of three migraine preventives under the Pharmaceutical Benefit Scheme (PBS). The selection of drugs for each of these medication trials necessarily includes a lucid discussion with the patient. The clinicians' expectations around tolerability, side-effects and likelihood of compliance in an individual patient help tailor general practitioner drug trial selection.

There have been few head-to-head comparisons amongst migraine preventives. At least one migraine preventive studied with a randomised-control trial (RCT) – topiramate – demonstrates similar efficacy to monoclonal antibodies directed at CGRP or its canonical receptor, if with a significantly higher likelihood of side-effects. As a result, real-world data suggest topiramate is often ceased.

An understanding of preventive drug options is vital in managing patients with migraine. Many patients benefit from these medications, even if responders cannot be predicted beforehand – precision medicine in migraine management is still some years away.¹⁹ A thorough accounting of these options is beyond the scope of this paper and readers are referred to other recent

reviews.^{4,6,12} Some patients do not respond to newer therapies and return to oral preventive drug trials with success; oral preventive treatment options still have an important therapeutic role.

Injectable therapeutics

OnabotulinumtoxinA

OnabotulinumtoxinA use in treatment for migraine is a systematised approach consisting of 31 injections of five units placed at set points around the head every 12 weeks, with an option to inject an additional 45 units in a follow-the-pain strategy. It has been approved for migraine under the PBS since 2014. To qualify, patients need to have CM, have failed or be unable to tolerate three migraine preventives, and demonstrate they are not overusing opioids, or at least have a strategy in-train to address this. Two cycles should be tried before efficacy can be determined. Patients need to have achieved a 50% or greater reduction from baseline in number of headache days per month to be eligible for continuing PBS subsidised treatment.

Robust data supporting its clinical use are extant. When assessed at 24 weeks, there was a statistically significant 8.4-day reduction in headache days per month compared with 6.6 days in the placebo arm.²⁰ A longer open label study found an average decrease of 10.7 headache days per month at 108 weeks with few adverse events.²¹ In responders, several quality-of-life indices improved in a sustained and often incrementally positive way.²²

Relative advantages of this treatment include it is an evidence-based procedure, the side-effect profile is excellent, there are no drug–drug interactions, and the intervention tends to be well tolerated. Problems include difficulties in accessing a neurologist and attending every 12 weeks, pragmatics that are especially burdensome for regional patients. Cost can be a significant barrier. There is a relative paucity of clinics associated with public hospitals providing the service.

Monoclonal antibodies directed at CGRP or its canonical receptor

The newest additions to migraine preventative agents are the CGRP monoclonal antibodies. Four monoclonal antibodies have been developed: one targeting the CGRP canonical receptor (erenumab) and three targeting the CGRP (epitinezumab, fremanezumab and galcanezumab). It appears that the CGRP pathway plays a dominant role in migraine and monoclonal antibodies; blocking CGRP has resulted in a positive treatment response.²³

These monoclonal antibodies were both tested and indicated in episodic and CM patient populations. The European headache federation²⁴ and American Headache Society²⁵ have developed their recommendations on the use of these monoclonal antibodies.

Currently, in Australia, galcanezumab and fremanezumab are available on the PBS for patients with CM that have failed, not tolerated or have contraindications to at least three preventative migraine medications. Private access will continue to be available for EM patients and for patients on erenumab. Epitezumab is currently approved by the Therapeutics Goods Administration and available in Australia. Practically, the current PBS criteria allows an initial 3-month treatment trial with either galcanezumab or fremanezumab. Continuing treatment is indicated if a 50% treatment response is achieved at 3 months. Galcanezumab is given as a loading dose of 240 mg subcutaneously then 120 mg monthly and is available as an auto-injector, which makes it patient-friendly to manipulate. Fremanezumab is used at 225 mg as a monthly injection under the PBS. Guidelines stipulate either medication not to be used in conjunction with onabotulinumtoxinA treatment prescribed under the PBS.

In the next section, the primary outcomes of four monoclonal antibodies trials are listed to reflect on the effectiveness of each monoclonal antibody and to also highlight that as a class effect, these agents have been effective. Two end-points are chosen: one is the change in monthly migraine days from baseline (per 12 weeks) and the other, 50% reduction from baseline in migraine days per month (50% responder rate). The data are divided into the episodic and CM cohort for each medication. These were double blind RCT.

In the EM cohort:

- With erenumab subcutaneous 140 mg/month, the change in monthly migraine days from baseline was -3.7 ± 0.2 at 6 months compared with placebo -1.8 ± 0.2 ; 50% responder rate was seen in 50% of the treated patients compared with 26.6% of the placebo patients.²⁶ This treatment response looks sustained at the 1-year²⁷ and 5-year follow up.²⁸
- With fremanezumab subcutaneous 225 mg/month, the change in monthly migraine days from baseline was -3.7 in the treated group and -2.2 in the placebo group at 3 months. The 50% responder rate was 44% in the treated group compared with 27.9% in the placebo group.²⁹
- With galcanezumab subcutaneous 120 mg/month, the change in monthly migraine days from baseline was -4.7 in the treated group and -2.8 in the placebo group. The 50% responder rate was 62.3% in the treated group compared with 38.6% in the placebo group³⁰ at 6 months.

- With eptinezumab at intravenous 300 mg/3 months, the change in monthly migraine days from baseline was -4.3 in the treated group compared with -3.2 in the placebo group at 3 months. The 50% responder rate was 56.3% in the treated group compared with 37.4% in the placebo group.³¹ At 1 year, the 50% responder group was 69.8% in the treated group and 55.4% in the placebo group.³² There is suggestion that the intravenous administration resulted in rapid attainment of clinical effects on day 1 of dosing as a consideration for its use.³³

In the CM cohort:

- With erenumab at 140 mg/month, the change in monthly migraine days from baseline was -6.6 compared with placebo group -4.2; the 50% responder rate was 41% in the treated group compared with 23% in the placebo group at 3 months.³⁴ At 52 weeks in the open label trial, the change in monthly migraine days from baseline was 6.7 and 50% responder rate was 67.3%.³⁵
- With fremanezumab at 225 mg/month, the change in monthly migraine days from baseline was -5.0 in the treated group compared with -3.2 in the placebo group. The 50% responder rate was 41% in the treated group compared with 18% in the placebo group³⁶ at 3 months.
- With galcanezumab at 120 mg/month, the change in monthly migraine days from baseline was -4.8 in the treated group compared with -2.7 in the placebo group. The 50% responder rate was 27.6% in the treated group compared with 15.4% in the placebo group at 3 months.³⁷
- With eptinezumab at 300 mg/3 months, the change in mean monthly migraine days was -8.2 in the treated group compared with -5.6 in the placebo group at 3 months. The 50% responder rate was 61.4% in the treated group compared with 39.3% in the placebo group.³⁸

Real-world Australian data with a larger, heterogenous population and more variability in comorbidities also reflected a change in monthly migraine days of -10.2 at 6 months and a 50% responder rate of 46.5% in the CM cohort with erenumab.³⁹ Patients with medication overuse and comorbid anxiety and depression have been shown to be responsive to these medications as well.^{40,41}

In terms of safety, approximately 55–67% of the trial group had adverse events reported. These adverse events were similar in the treated and placebo group. Injection site pain, injection site induration, injection site erythema

Box 2 Preventives used in migraines

- A. Oral preventives: propranolol, amitriptyline, pizotifen, candesartan, nortriptyline, sodium valproate, topiramate.
- B. OnabotulinumtoxinA.
- C. CGRP monoclonal antibodies: galcanezumab, fremanezumab, erenumab, eptinezumab.

were the largest reported adverse events (up to 30%),²⁹ of which 3–5% were severe enough for discontinuation.⁴² The rates of vascular and non-vascular adverse effects were similar across placebo and treated groups.^{28,43}

There are other theoretical concerns as CGRP is widely expressed throughout the body and off-target effects may be possible.⁴⁴ There is a current Australian CGRP monoclonal antibody adverse effects data collection. Real-world monitoring is occurring using the FDA Adverse Events Reporting System that identified an association between hypertension and the use of erenumab.⁴⁵ This might be a class effect and blood pressure should be routinely monitored. One relatively conservative current consensus suggests that these should not be used in pregnant or nursing women, individuals with alcohol or drug abuse, cardiovascular and cerebrovascular diseases or a severe mental disorder.²⁴

Conclusion

The principal barriers around optimising migraine management for Australians are recognition and education of clinicians and patients alike. For most migraine sufferers, simple interventions will be adequate. Preventive options for those patients with a more significant burden of disability and discomfort have expanded markedly in the past several years. OnabotulinumtoxinA has demonstrated very useful efficacy in this group.

The availability of monoclonal antibody treatments, which are migraine specific, well tolerated and now government subsidised, has meant that there are more options for migraine sufferers (Box 2).⁶

Acknowledgements

Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

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