Migraine prophylaxis

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The evolution of the triptans encouraged the hope that practical new treatments for migraine would continue to appear regularly. Better understanding of migraine pathophysiology (especially the role of 5-$HT_{1B/1D}$ receptors, neuropeptides and trigeminovascular inflammatory processes)[1,2] has enabled rational development of drugs designed to treat migraine attacks, but despite promising preliminary results,[3,4] such agents are yet to appear in routine clinical practice. By contrast, no models of migraine have allowed the efficient development of effective prophylactic agents; these generally appear on the market for migraine after establishing themselves for other indications such as hypertension or epilepsy. As a result, confirmation that such agents are useful for migraine tends to occur later in their commercial lifespan. Nevertheless, there have been some exciting developments in migraine prevention.

ABSTRACT

- There is a wide array of options for migraine prophylaxis; many of the available drugs are clearly proven to be effective and yet are underused in Australia.
- "New" drugs which are gaining favour for migraine prophylaxis include topiramate, candesartan, gabapentin and botulinum toxin. The evidence for efficacy is excellent for topiramate and reasonably good but limited for candesartan and gabapentin. The use of botulinum toxin is controversial and has gained substantial popularity through anecdotal experience rather than convincing published evidence.
- Transformed or chronic migraine with medication overuse is a particularly difficult problem. New strategies to aid in medication withdrawal are reviewed.
- The approach to menstrual migraine and migraine with prominent aura may differ from that for typical migraine. Novel approaches are being explored for these problems.

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Prophylaxis in general

Australian Therapeutic Guidelines recommend regular preventive treatment for patients who continue to experience more than two or three acute attacks of migraine per month.[5] Other experts highlight that prophylaxis may be warranted in some patients with a lower attack frequency if they have prolonged or disabling attacks.[6] Patient preference should, of course, always be considered.

Influential evidence-based reviews of migraine treatment have been published by both the American Academy of Neurology[7] and the European Federation of Neurological Societies.[8] Although there are many prophylactic agents with established efficacy, Australian general practitioners restrict their choice, in most cases, to pizotifen or propranolol.[9]

There is a bewildering array of options for migraine prophylaxis (Box 1). Many of the available drugs are clearly proven to be effective and yet are underused in Australia.[9] Many neurologists use a personal algorithm in deciding the order in which drugs could be used in a particular patient (Box 2, Box 3). As a rule, each prophylactic drug tried should be given for long enough to establish its effect. This may take about 3 months. Use of ineffective drugs should be discontinued, and other drugs considered.

What's new?

A number of new options have appeared in recent years. In brief, topiramate is now a thoroughly established agent, and is listed on the Pharmaceutical Benefits Scheme (PBS) as a second-line option, after propranolol and pizotifen. Candesartan is very well tolerated by most patients and is attractive when previous agents have produced unacceptable side effects. Lisinopril seems to have few advantages over candesartan, and gabapentin is expensive; neither drug is widely used for migraine in Australia. The depth of data supporting the effectiveness of candesartan, lisinopril and gabapentin is limited; replication of the results quoted below would enhance confidence in these drugs. Botulinum toxin is also expensive and doubts remain about its efficacy. However, its adverse event profile is excellent and, anecdotally (and from published case series), it seems that some patients respond dramatically.

New drugs for prophylaxis

Topiramate

This is a relatively new anticonvulsant medication, and there have been three large randomised controlled trials which have shown efficacy. One randomised study of 483 patients showed that mean number of migraine days per month was significantly reduced with topiramate at daily doses of 100 mg (by 2.1 days) and 200 mg (by 2.4 days) compared with placebo (1.1 days).[11] This effect was noted within the first month of treatment and persisted for the 26-week trial period. There was a also a trend towards improvement in the 50 mg group in this study. Adverse events leading to cessation of topiramate therapy included paraesthesia, fatigue, nausea and weight loss.[11] Almost identical results were found in another large study[12] and a smaller one.[13] These data were analysed by a Cochrane review and found to be convincing.[14] A further large study found similar efficacy to propranolol.[15] Continuing benefit was demonstrated when patients who had been treated with topiramate for 6 months were randomly assigned to continue topiramate therapy or placebo over the next 6 months; headache days per 4 weeks increased by 1.19 with placebo and 0.10 with topiramate.[16] Of note is the consistently reported side effect of weight loss with topiramate, in contrast to the weight gain often seen with such established medications as sodium valproate and pizotifen.

In practice, in the past couple of years, before its PBS listing in Australia, topiramate has been an attractive choice when other older agents have failed, and especially when the patient is overweight. The PBS listing provides subsidised treatment for migraine prevention only when both pizotifen and β-blockers are contraindicated or not tolerated. This results in the bizarre situation that inefficacy of these previous treatments is not sufficient to qualify for PBS subsidy. The PBS decision is based on lack of

1 Commonly used prophylactic agents for migraine: properties, regulatory status, and evidence for their use

Drug	Dose	Typical/important side effects	Original use	Mode of action*	Regulatory status		Guidelines			Level of evidence†
					TGA	PBS	AAN[7]	EFNS[8]	TG[5]	
Propranolol	40–120 mg twice daily	Fatigue, postural dizziness, caution in reversible airways disease, PVD and CCF	Anti-hypertensive	β-blocker	+	GM	Level 1	A	Y	E1
Sodium valproate	400–600 mg twice daily	Weight gain, drowsiness, hair loss, hepatic and haematological dysfunction, teratogenic	Anti-convulsant	State-dependent sodium-channel blockade and GABA-ergic effect	–	GO	Level 1	A	Y	E1
Topiramate	25–100 mg twice daily	Confusion, paraesthesias, weight loss, renal stones, secondary angle closure glaucoma	Anti-convulsant	State-dependent sodium-channel blockade and GABA-ergic effect; kainate/AMPA-receptor antagonist	+	AM	Level 1‡	A	Y	E1
Amitriptyline	10–75 mg nightly	Drowsiness, dry mouth and other anticholinergic effects	Tricyclic antidepressant	Noradrenaline and 5-HT-uptake inhibitor	–	GO	Level 1	B	Y	E1
Candesartan	16 mg daily	Hypotension, hyperkalaemia	Anti-hypertensive	Angiotensin II receptor antagonist	–	GO	Level 2	C		E2
Lisinopril	20 mg daily	Cough, hypotension, hyperkalaemia	Anti-hypertensive	Angiotensin-converting enzyme inhibitor	–	GO	Not rated	C		E2
Verapamil	160–320 mg daily	Constipation, ankle swelling, cardiac conduction abnormalities	Anti-hypertensive	Calcium-channel blocker	–	GO	Level 2	NR	Y	E2
Metoprolol	50 mg twice daily	Hypotension, bradycardia, cold extremities, fatigue, dizziness, dreams	Anti-hypertensive	β-blocker	+	GM	Level 2	A		E2
Gabapentin	900–3600 mg daily	Dizziness, sedation	Anti-convulsant	Effect on α-2-δ subunit of voltage-gated calcium channels	–	AO	Level 2	C		E2
Cypro-heptadine	4–12 mg daily	Somnolence, dry mouth, gastrointestinal upset, urinary retention	Anti-histamine	5-HT and histamine antagonist with anticholinergic and sedative effects	+	RM	Level 3	NR		E2
Methysergide	1–4 mg daily	Drowsiness, leg cramps, retroperitoneal fibrosis	Migraine	5-HT antagonist and vasoconstrictor	+	GM	Level 4	C	Y	E2
Pizotifen	0.5–2 mg daily	Weight gain, drowsiness	Migraine	5-HT antagonist with some antihistamine, properties	+	GM	Not rated	D	Y	E2
Clonidine	50 mg wice daily	Drowsiness, dry mouth, nausea	Anti-hypertensive	Central α2-adrenergic stimulation	+	GM	Level 5	D		E2

PVD = peripheral vascular disease. CCF = congestive cardiac failure. GABA = γ-aminobutyric acid. AMPA = D,L-α-amino-3-hydroxy-5-methyl-isoxazole propionic acid. TGA = Therapeutic Goods Administration: + = TGA-approved for migraine; – = Not TGA-approved for migraine. PBS = Pharmaceutical Benefits Scheme: GM = PBS general benefit for migraine; RM = PBS restricted benefit for migraine; AM = PBS authority required for migraine; GO = PBS general benefit (other indications); AO = PBS authority required (other indications). AAN = American Academy of Neurology: "Level" denotes levels of evidence from 1 (best) to 5 (worst); some levels are modified by the drug's adverse event profile. EFNS = European Federation of Neurological Societies: A = drugs of first choice; B = drugs of second choice; C = drugs of third choice; D = not recommended; NR = no recommendation. TG = Australian Therapeutic Guidelines: Y = listed as an appropriate agent.

* In most cases, actions are multiple, and those responsible for effect in migraine are unknown or speculative. † National Health and Medical Research Council levels of evidence.[10] ‡ According to revised version of the AAN guidelines, currently in press (Stephen Silberstein, Professor of Neurology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pa, USA, personal communication). ◆

scientific evidence that topiramate is effective when other agents have failed, despite widespread anecdotal experience that this is often the case. Consequently, topiramate may be used in Australia according to the PBS guidelines or prescribed for suitable patients outside PBS guidelines and without PBS subsidy.

Side effects are mostly dose-related, and are less troublesome when topiramate is used for migraine than for epilepsy, as the doses are typically lower (100 mg per day compared with 200–400 mg per day). Side effects include drowsiness, dizziness, somnolence and an unusual problem with word-finding, paraesthesiae in hands and feet, and reduced appetite and weight loss.

Candesartan

A randomised, double-blind, crossover study of candesartan (16 mg daily) versus placebo has been performed.[17] The mean number of days with headache in 12 weeks (the primary endpoint) was 18.5 with placebo versus 13.6 with candesartan ($P = 0.001$; $n = 57$). Several secondary endpoints also favoured candesartan, and 32% of patients had a greater than 50% reduction in migraines while taking candesartan compared with the period taking placebo. The drug was well tolerated — adverse events were similar in the two periods. Candesartan is starting to be used more widely by Australian neurologists, some of whom are enthusiastic proponents.

Lisinopril

An earlier study had shown a clear benefit from the angiotensin-converting enzyme (ACE) inhibitor lisinopril (at a dose of 20 mg).[18] The number of days with headache was reduced by 17% compared with the placebo arm; this benefit was somewhat less than in the later trial of candesartan,[17] and adverse events, including cough, were more often an issue. ACE inhibitors are not widely used in Australia for migraine prophylaxis.

The clinical efficacy of ACE and angiotensin II inhibitors supports a role for the renin–angiotensin system in migraine. The benefits of these drugs are thought not to derive from the effect on blood pressure, but perhaps modulation of receptors in the central nervous system.[19]

Gabapentin

One group studied gabapentin, titrated to a dose of 2400 mg per day.[20] An unusual statistical approach with analysis of "modified intention to treat" populations detracts from this study. After 12 weeks of treatment, the median 4-week migraine rate was 2.7 for the patients treated with gabapentin and 3.5 for those taking placebo ($P = 0.006$), down from 4.2 and 4.1, respectively, during the baseline period. Additionally, 26 of 56 patients (46.4%) receiving a stable dose of 2400 mg of gabapentin per day and five of 31 patients (16.1%) receiving placebo showed at least a 50% reduction in the 4-week migraine rate ($P = 0.008$). Adverse events considered to be drug-related (especially somnolence and dizziness) resulted in 13 of 98 gabapentin-treated patients (13.3%) and three of 45 placebo-treated patients (6.7%) withdrawing from the study.

Botulinum toxin

The use of botulinum toxin for migraine prophylaxis is particularly controversial. Large case series have been reported, with several experienced and respected experts convinced that this treatment is effective, at least in selected patients. Indeed, botulinum toxin has become a standard treatment option in many centres.[21] This is despite the fact that several high-quality trials have failed to show effectiveness of botulinum toxin. Discussion of the data and of the paradox offers one possible explanation that a subgroup of non-responders is so large as to render the published trials underpowered.[22] Recent studies suggest that headaches described as "imploding" or "ocular" may respond while "exploding" headaches may not.[23] Independent prospective verification of this hypothesis is required.

Personal experience (RJS) suggests that, in a cohort of difficult and otherwise unresponsive patients, about 10% have a dramatic response and another 30% have a worthwhile response. Some case series claim an even higher response rate.[21]

2 Use of established drugs

- Propranolol would often be the drug of first choice unless the patient had asthma; some patients tolerate β-blockers poorly and others fail to respond.
- Pizotifen may be a suitable next choice: it is widely used so general practitioners are familiar with it. Drowsiness can usually be avoided by careful dose titration, but weight gain makes it an unattractive option for many patients. Migraine with prominent vestibular features seems to respond especially well to pizotifen.
- With the current Pharmaceutical Benefits Scheme restrictions on topiramate (see text), it is vital to document the basis for considering prescribing topiramate for patients in whom propranolol and pizotifen have failed, especially if the failure was due to side effects.
- Amitriptyline is widely used as a modifier of chronic pain, and has particular attraction where migraine is associated with other painful conditions (for example, exacerbation of migraine after a whiplash injury). The side effects of tricyclic antidepressants are well known, but the doses used for migraine are relatively low and most patients tolerate them.
- Sodium valproate is likewise used in relatively small doses for migraine, and the most problematic side effect is weight gain.
- Cyproheptadine is used infrequently and seems to have few advantages over pizotifen, which is probably similar in its mode of action.
- Clonidine was found to be effective in early trials, but later studies have cast doubt on their findings. Anecdotally, it is usually ineffective, but occasional patients who are resistant to other agents seem to respond, so some neurologists are prepared to try it briefly in difficult patients.
- Verapamil is not often used in typical migraine, but may be used when aura symptoms are prominent.
- Methysergide is considered to be the most potent of all these agents, and may be effective when all else fails. Its use is limited by concerns about retroperitoneal fibrosis and related disorders. It must be withdrawn for at least a month after every 6 months (at most) of continuous use; the withdrawal should be gradual to avoid rebound exacerbation of migraine. Even so, some patients have a very difficult time in the month off; the best way to manage this remains unclear. ◆

Special circumstances

Migraine with medication overuse

Chronic daily headache, defined as headache on more than 15 days per month with more than 4 hours of headache on each of these days, is common, occurring in 4% of the population.[24] Most

3 Migraine prophylactic agents: factors in deciding which to prescribe

	Patient						
Drug*	Has asthma	Overweight	Prominent aura	Chronic non-headache pain also	Hypertension also	Cost is an issue	Intractable migraine despite many attempts at prophylaxis
Propranolol	×××		×		++		
Pizotifen		××					
Sodium valproate		××	++				
Topiramate		+++				× (if not PBS eligible)	
Amitriptyline		×		++			
Candesartan					++		
Lisinopril					++		
Verapamil			++		++		
Metoprolol	×				++		
Gabapentin				+ (if neuropathic pain)		××	
Cyproheptadine		×					
Methysergide							+++
Clonidine					+		+
Botulinum toxin						×××	++
Lamotrigine			+			××	
Levetiracetam			+			××	

Contraindications to the drug: × = relative; ×× = moderate; ××× = strong. Points in favour of the drug: + = mild; ++ = moderate; +++ = strong.
* Listed in an order in which they might be chosen in Australia if there were no particular contraindications to or points in favour of any drug. ◆

cases troublesome enough to be referred to headache clinics arise from migraine,[25] with transformation over time from an episodic to a very frequent or daily pattern. This situation has been termed "transformed migraine" or "chronic migraine"; there are recently published criteria for the diagnosis of "chronic migraine".[26] There is controversy as to the cause of this transformation, with some experts believing it very often occurs because of medication overuse, resulting in "rebound" headaches, while others feel that the pattern generally evolves spontaneously with more frequent medication use as a consequence.[27] The truth probably lies between these positions; headaches in some patients certainly reduce dramatically once overused medications are withdrawn, while in others, they do not. All experts would agree that an escalating pattern of migraine frequency requires active intervention, and this generally involves minimising the regular use of acute treatments, particularly certain agents, and aggressively pursuing prophylaxis. This approach has led to guidelines on or recommendations for the maximum desirable frequency of use of various acute agents (Box 4).[28,29]

4 Guidelines on the maximum desirable frequency of use of various agents for treating acute headache in patients with frequent migraine

Drug	Diener et al[28]	Based on International Headache Society criteria for overuse[29]
Ergotamine	< 4 mg/attack, < twice/week, < 20 mg/month	< 10 days/month
Triptans	< 10 doses/month	< 10 days/month
Codeine	Avoid	< 10 days/month
Simple analgesics	No comment	< 15 days/month
Caffeine	Avoid	< 15 days/month

Once a pattern of chronic daily headache with medication overuse is established, it is necessary to withdraw the offending agent. Numerous protocols to aid successful withdrawal by controlling the inevitable exacerbation of headache have been proposed, supported by case series, but high-quality trials are lacking. Outpatient withdrawal may be effective on occasions, but for patients overusing codeine or substantial amounts of ergotamine or triptans, inpatient management is preferred.[28]

Agents used to aid medication withdrawal have included analgesics, tranquilisers, neuroleptics, amitriptyline, naproxen and valproate. Naproxen was shown to be better than symptomatic treatment with antiemetics and analgesics.[30]

The usual approach to inpatient management has included the use of fluid replacement and intravenous dihydroergotamine.

What's new?

A large open-label study supports the use of high dose prednisolone (60 mg/day) to aid with outpatient medication withdrawal.[31] A smaller placebo-controlled study of prednisone showed that it reduced the total number of hours with severe or moderate headache within the first 72 and 120 hours of withdrawal.[32] The use of intravenous lignocaine for the most difficult patients has been reported in a large open-label study from Australia.[33] This approach is gaining favour internationally.[34]

Two recent studies of topiramate use in chronic migraine have produced similar results, even though one included patients with medication-overuse headache[35] and the other excluded them.[36] In the study including medication-overuse patients, the reduction in migraine days per month was 3.5 days irrespective of medication overuse, while there was no reduction with placebo.[36]

Menstrual migraine

Many women with migraine have menstrually associated migraine (MAM). A subgroup of patients have attacks that occur exclusively with or just before menses: this is called "true menstrual migraine" and occurs in about 15% of women who have migraines.

Patients in whom most of the disabling attacks occur in relation to menstruation may benefit from the strategy of "miniprophylaxis", in which a preventive medication is used for about a week at the time of vulnerability. Drugs used in practice in this way have included oestrogens, non-steroidal anti-inflammatory drugs, ergotamine, dihydroergotamine, methysergide and magnesium,[37] but there have been few well designed studies. Triptans have also been used: there is an open-label study of 20 women with MAM given oral sumatriptan (25 mg thrice daily) and a small double-blind, placebo-controlled study of naratriptan (1 mg and 2.5 mg daily).[38] In both cases the findings were positive, but curiously only for the lower dose of naratriptan.

What's new?

A large (546 participants) randomised, double-blind, placebo-controlled study of frovatriptan (2.5 mg daily or twice daily for 6 days beginning 2 days before the start of menstruation) has been reported.[37] The incidence of MAM headache during the 6-day perimenstrual period was significantly reduced compared with placebo (67% for placebo; 52% for frovatriptan 2.5 mg daily; 41% for frovatriptan 2.5 mg twice daily). Both frovatriptan regimens also reduced the severity and duration of MAM, and the use of rescue medication.

Frovatriptan is a long-acting triptan making it theoretically suitable for a prophylactic role, but it is not currently available in Australia. Of the triptans on the market here, naratriptan has the longest half-life, and its use in this context has some published support.[38]

Prominent or prolonged aura

Migraine aura is now recognised as a primarily neural event, involving spreading depression of activity, with secondary reduction in cerebral blood flow rather than a vascular or vasospastic process. In some patients, the aura symptoms predominate, with mild or no headache, or may be unusually prolonged. Prevention of such episodes may require a different approach from that used for more typical migraine. The information on this point has, however, been anecdotal.

A 2001 survey of North American neurologists found that verapamil and valproate were the preferred treatments, with verapamil especially popular for prolonged aura.[39] β-Blockers were rarely used, perhaps because of concerns about limited compensatory vasodilator capacitance.[39]

What's new?

There are recent open-label studies suggesting substantial benefit in aura prevention from the new anticonvulsant lamotrigine,[40,41] and a small study raising the possibility of benefit from levetiracetam.[42] These drugs are currently available on the PBS in Australia only for epilepsy.

Impediments to new and emerging treatments in Australia

Prophylactic agents for migraine tend to appear late in the commercial life of the drugs concerned. Many effective agents are out of patent, or nearly so, and there is little incentive for the manufacturers to pursue TGA approval for use in treating migraine. This leads to prescribers having to write such prescriptions "off-label", which some are reluctant to do. In the recent case of topiramate, for which TGA and PBS approval have been requested, the PBS guidelines, while doubtless justifiable from the evidence provided, result in a bizarre situation — some patients who benefit from the drug, but not from cheaper alternatives, are denied subsidy because the earlier drugs were ineffective rather than intolerable.

Competing interests

Richard Stark has acted as a consultant to Janssen-Cilag and Allergan, and has received speaker fees from Janssen-Cilag.

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