

Pharmacological prevention of migraine

Nathan Fenstermacher, Morris Levin, Thomas Ward

Dartmouth Headache Centre,
Dartmouth Hitchcock Medical
Centre, Lebanon, NH 03756, USA

Correspondence to:
N Fenstermacher
nathan.p.fenstermacher@hitchcock.org

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People who have migraine experience intermittent attacks of unilateral, pulsating, and moderate to severe headache with associated nausea or photophobia and phonophobia (or all these symptoms). These attacks typically start before the age of 40, often in childhood or teenage years, and occur most commonly from the second to the fourth decade of life.¹ Attacks may be infrequent or frequent. Chronic migraine is diagnosed when attacks regularly occur on more than 15 days a month. Box 1 shows the International Headache Society's classification criteria for migraine without aura.

Recent population studies have shown the worldwide prevalence of migraine to be greater than 10%. The prevalence of migraine in the United States has been estimated at 18% for women, 6% for men, and 12% overall.²⁻³ Migraine clearly affects women more than men, and its aetiology also seems to have a hereditary component. The World Health Organization ranks migraine 19th on the list of diseases worldwide that cause disability.^{w1} In spite of recent advances in treatment options for migraine, both acute and preventive, these treatments continue to be underused,³⁻⁴ which leaves patients with unnecessary suffering and increases the burden on the healthcare system. We review the different types of preventive treatment and discuss how they should be used to treat migraine effectively.

When to consider prevention for migraine

Specific clinical guidelines on when it is clinically appropriate to start preventive treatment vary between different countries and organisations. A high frequency of migraine, inadequate responsiveness to drugs used to treat migraine acutely, and migraines that greatly interfere with activities of daily life are accepted criteria for starting preventive treatment.⁵⁻⁷ Box 2 lists the European Federation of Neurological Societies and American Academy of Neurology guidelines for starting preventive treatment. It is important to consider coexisting medical conditions and psychological diagnoses when deciding on a preventive treatment. A single drug may effectively treat the coexisting condition and prevent migraines in some

SOURCES AND SELECTION CRITERIA

The content of this article is based in part on guidelines from the United States Headache Consortium, which use an evidence based medicine format but include data up to 1997 only.⁵ These guidelines are available at the American Academy of Neurology website (www.aan.com). We also included guidelines on the management of migraine from the European Federation of Neurological Societies.⁶⁻⁷ In addition, we used Cochrane reviews as well as peer reviewed publications in headache and neurological journals obtained from Medline searches.

circumstances. The importance of the discussion between practitioner and patient about preventive drugs and the reasons for considering their use is often overlooked. Shared decision making, which ensures that the patient understands the reasons for starting preventive treatment and feels comfortable with the drug chosen, increases the likelihood of adherence to the preventive treatment plan. Because overuse of analgesics and other acute drugs may make preventive drugs less effective, the patient should also be instructed to limit their use.⁸ Simple analgesics

Box 1 | International Headache Society's classification criteria for migraine without aura¹

At least five attacks fulfilling criteria A-C

A: Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

B: Headache has at least two of the following characteristics:

- Unilateral location
- Pulsating quality
- Moderate or severe pain intensity
- Aggravation by, or causes avoidance of, routine physical activity

C: During headache at least one of the following occurs:

- Nausea or vomiting
- Photophobia and phonophobia

D Not attributed to another disorder

Box 2 | Criteria for starting preventive treatment^{6,7}

Quality of life, business duties, or school attendance is severely impaired

Two or more attacks a month

Migraine attacks do not respond to acute drug treatment

Frequent, very long, or uncomfortable auras occur

SUMMARY POINTS

Accurate diagnosis of migraine is crucial to establishing an effective treatment plan

Migraine cannot be cured, just prevented

A preventive management plan must take into account coexisting conditions and the patient's preferences

Preventive treatment should aim to decrease the frequency and severity of acute attacks, make acute treatments more efficacious, and minimise adverse drug reactions

Drugs for the prevention of migraine

Drug	Target dose*	Common adverse drug reactions	Strength of evidence (US)†	Strength of evidence (Europe)‡
β blockers				
Propranolol	80-160 mg QD	Hypotension	A	A
Metoprolol	25-100 mg QD-BID	Hypotension	B	A
Atenolol	25-100mg QD	Hypotension	B	NA
Calcium channel blockers				
Flunarizine	5-15 mg QD	Weight gain, tardive dyskinesia	NA	A
Verapamil	80-120 mg QD-TID	Bradycardia, hypotension	B	NA
Amlodipine	5-10 mg QD	Oedema	NA	NA
Other antihypertensives				
Lisinopril	20 mg QD	Cough	NA	C
Candesartan	16 mg QD		NA	C
Antidepressants				
Amitriptyline	25-75 mg QD	Anticholinergic side effects	A	B
Nortriptyline	10-100 mg QD	Anticholinergic side effects	C	NA
Fluoxetine	10-40 mg QD		B	NA
Venlafaxine	75-150 mg BID	Drowsiness, urinary retention	NA	B
Anticonvulsants				
Valproate	250-500 mg BID	Weight gain, tremor, hair loss	A	A
Topiramate	50-100 mg BID	Nephrolithiasis, acute glaucoma	A	A
Gabapentin	300-1200 mg TID	Drowsiness, dizziness	B	C
Lamotrigine	50-300 mg QD	Stevens-Johnson syndrome	NA	NA
Zonisamide	25-400 mg QD	Nephrolithiasis, sulfonamide allergy	NA	NA
Supplements and herbs				
Riboflavin	200 mg BID		B	C
Coenzyme Q10	100 mg TID	Gastrointestinal upset	NA	C
Magnesium	400-600 mg QD	Diarrhoea	B	C
Others				
Methysergide	2 mg QD	Retroperitoneal fibrosis	A	
OnabotulinumtoxinA	155 U		A	

*QD=once daily; BID=twice daily; TID=three times daily.

†Taken from American Academy of Neurology practice parameter.

‡Taken from European Federation of Neurological Societies guidelines.

should ideally be used on fewer than 15 days a month and combination analgesics and other acute drugs be limited to 10 days a month.^{w2}

What are the goals of preventive treatment?

The goals of preventive treatment mirror the criteria for starting these drugs. The major targets of preventive treatment are reduced frequency and severity of migraine headaches, and it is helpful to communicate this to the patient.⁵⁻⁷ An important point to stress early on is that migraine has no cure, and the goal is to manage and reduce the burden of the disease. The patient's disability is reduced if these main goals are achieved. Other goals of preventive treatment include reduced use of acute drugs and fewer visits to the emergency room or doctor's surgery. Patients also need to understand that it may take time for a drug to become effective, most often two to three months at an adequate dose. Asking patients to keep a headache calendar or diary is an effective way to monitor progress.

What do the treatments prevent?

The pathogenesis of migraine is not completely understood. Studies of patients prescribed commonly used drugs for preventing migraine have shown that these drugs suppress cortical spreading depression.^{w3} However the complex mechanisms of action of migraine preventive drugs are unclear.

What drugs are available for the prevention of migraine?

Although preventive options for migraine may be either pharmacological or non-pharmacological, we will discuss the pharmacological option only. Certain β blockers, calcium channel blockers, tricyclic antidepressants, and antiepileptic drugs are considered first line preventive treatments, and many other drugs are considered second and third line options.⁵ Only five drugs are currently approved by the Food and Drug Administration (FDA) for prevention of episodic migraine. These are propranolol, timolol, valproate, topiramate, and methysergide. OnabotulinumtoxinA (Botox) is now FDA approved for the treatment of chronic migraine. European and US treatment recommendations have only a few minor differences (table).⁵⁻⁶ The evidence for the recommendations is derived from clinical trials where available.

β blockers

Propranolol and metoprolol have been evaluated in randomised placebo controlled trials for their efficacy in migraine prevention. A Cochrane review of available studies in 2004 concluded that propranolol is effective in preventing migraines in the short term, with insufficient data to make a conclusion regarding long term treatment.⁹ Sustained release options offer the benefits of once daily dosing and improved compliance. β blockers are a good choice of preventive drug for patients with coexistent hypertension, but they should not be used for patients with asthma and must be used with caution in patients with depression.

Calcium channel blockers

Flunarizine—a calcium channel blocker not available in all countries—causes a mild reduction in the frequency of migraine attacks.¹⁰ Calcium channel blockers that are more widely available, such as amlodipine and verapamil, are effective options for some patients.^{w4} As with most other antihypertensive drugs, hypotension and pedal oedema are side effects to watch out for, but otherwise these drugs are well tolerated.

Other antihypertensive drugs

Several drugs belonging to the angiotensin converting enzyme inhibitor class and the angiotensin receptor blocker class have been studied as potential treatments for preventing migraine, although because of a lack of definitive data for migraine prevention, these drugs are second or third tier options. A randomised, placebo controlled, crossover study showed that lisinopril, an angiotensin converting enzyme inhibitor, decreased both the number of days with migraine and headache severity by 20%.¹¹ One randomised controlled trial found that candesartan, an angiotensin receptor blocker, reduced the number of days of migraine a month by nearly five days compared with placebo.¹² Both these classes of drugs may be alternative choices for patients with or without hypertension who do not tolerate, or do not respond to, β blockers or calcium channel blockers.

Antidepressants

Amitriptyline, a tricyclic antidepressant, has been shown to be effective in preventing migraine in several randomised controlled trials and is considered a first line option in the

TIPS FOR NON-SPECIALISTS

- When choosing a preventive drug, carefully consider treating coexisting conditions with the same drug, if appropriate
- To improve treatment adherence, take the time to explain the rationale for starting preventive drugs to the patient and answer any questions
- Limit polypharmacy if possible; however, multiple drugs may be needed
- Limit the use of analgesic drugs because current evidence suggests that when analgesic use is high, preventive drugs are less effective

ADDITIONAL EDUCATIONAL RESOURCES

All the resources below provide more information on classification and treatment options in a clear and concise manner as well as links to other resources

Resources for clinician

International Headache Society (www.ihs-headache.org)

American Headache Society (www.americanheadachesociety.org)

European Headache Federation (www.ehf-org.org)

British Association for the Study of Headache (www.bash.org.uk)

European Federation of Neurological Societies (www.efns.org)

Resources for patients

American Headache Society (www.achenet.org)

Migraine Action Association (www.migraine.org.uk)

World Headache Alliance (www.w-h-a.org/)

US.¹³ The dose of amitriptyline used to prevent migraine is lower than the recommended dose to treat depression, and benefits in migraine are independent of improvement in depression. The effective use of other tricyclics, such as protriptyline and nortriptyline, has been reported, but high level evidence to support their use is lacking. Patients may experience anticholinergic side effects such as dry mouth and constipation when taking tricyclic drugs. Selective serotonin reuptake inhibitors have proved to be no more effective than placebo for preventing migraine attacks.¹⁴ The serotonin and noradrenaline reuptake inhibitor venlafaxine has been shown to be effective in prevention of migraine compared with placebo and selective serotonin reuptake inhibitors. One randomised controlled trial found that venlafaxine decreased the number of days with migraine compared with placebo.¹⁵ Serotonin and noradrenaline reuptake inhibitors may be appropriate for patients with chronic pain from other conditions, such as fibromyalgia.

Antiepileptic drugs

Several antiepileptic drugs have been shown to be effective in preventing migraine in randomised controlled trials, and valproate and topiramate are generally considered first line treatment choices since a Cochrane review in 2008 found them to be effective.¹⁶⁻¹⁹ The same Cochrane review also concluded that the class as a whole is generally well tolerated and can help reduce the frequency of migraine attacks.¹⁷ Valproate must be used with caution in women of childbearing age because of its association with neural tube defects in offspring. Warn patients about weight gain, hair loss, and tremor when prescribing valproate. Topiramate

has been associated with weight loss.¹⁸ A history of renal stones is a relative contraindication for using topiramate. Topiramate may be effective in treating chronic migraine and may be useful in patients whose headaches are complicated by overuse of acute drugs.^{w5} The evidence that gabapentin is effective in preventing migraine is variable, and it is not considered a first line treatment choice. Gabapentin is helpful for patients with other pain conditions, but it has to be taken three times a day. Lamotrigine may be useful for patients who have migraine with aura.^{w6}

Supplements and herbs

Several vitamins, minerals, and herbal remedies can be used to prevent migraine and may appeal to patients who wish to avoid taking daily prescription drugs. These treatments offer the benefits of few adverse drug reactions and drug interactions. Butterbur, or *Petasites hybridus*, is effective but warn patients to use only properly processed plant extracts because the leaves of the plant are potentially carcinogenic. Petasites decreases the frequency of migraine attack, and one study found a statistically significant decrease ($\geq 50\%$) in the frequency of migraine.¹⁹ Coenzyme Q10 can decrease the frequency of attacks, but it has little effect on the severity of migraine and does not reduce the use of acute drugs.²⁰ Magnesium oxide and riboflavin (vitamin B-2) have also been shown to reduce the frequency of attacks.²¹⁻²² A negative Cochrane systematic review and meta-analysis of studies that examined the effectiveness of feverfew, derived from the *Tanacetum parthenium* plant, has limited its use.²³

Other drugs

Methysergide, an ergot derivative, is an effective preventive option. Its use is limited to six month periods with recommended drug holidays because of the potential development of retroperitoneal, pleural, and cardiac valve fibrosis. Although it was approved by the FDA for prevention of migraine, methysergide is no longer available in the US. Its major metabolite, methylergonovine, is however used by some practitioners.

Botulinum toxin A

The use of botulinum toxin A has gained a great deal of attention in recent years. The results of trials to date have not proved clear efficacy over placebo in episodic migraine, and it is known to be ineffective for tension-type headache.²⁴⁻²⁷ However, the FDA has approved botulinum toxin A for the treatment of patients with chronic migraine, and it is licensed in the United Kingdom for the same indication.²⁵ It is administered every three months as 155 units distributed over 31 injection sites, which include the forehead, temporalis muscles, suboccipital areas, upper posterior cervical musculature, and trapezius muscles.

Combination treatment

For patients who fail to respond to single preventive drugs, the use of more than one drug may prove effective—for example, a combination of propranolol and amitriptyline.

When should preventive treatment be discontinued?

The frequency of follow-up visits is tailored to the patient's individual needs and response to treatment. Guidelines for

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The pain and the pressure: a film about latest research into the causes of this debilitating condition.

bmj.com Previous articles in this series

▶ The risks of radiation exposure related to diagnostic imaging and how to minimise them (*BMJ* 2011;342:d947)

▶ Telehealthcare for long term conditions (*BMJ* 2011;342:d120)

▶ Preventing exacerbations in chronic obstructive pulmonary disease (*BMJ* 2011;342:c7207)

▶ Islet transplantation in type 1 diabetes (*BMJ* 2011;342:d217)

▶ Diagnosis and management of hereditary haemochromatosis (*BMJ* 2011;342:c7251)

discontinuing preventive drugs are arbitrary, and treatment decisions should be made on a case by case basis. For example, if coexisting conditions are being treated, the clinician might decide not to discontinue drugs. Drugs might need to be discontinued slowly in patients who react to quick changes in medication. Drugs are usually discontinued in patients who have shown no clear benefit after an adequate trial duration.

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Provenance and peer review: Commissioned; externally peer reviewed.

- 1 Headache Classification Committee of the International Headache Society. The international classification of headache disorders. 2nd ed. *Cephalalgia* 2004;24(suppl 1):1-160.
- 2 Silberstein SD, Lipton RB, Dodick DW. Wolff's headache and other head pain. 8th ed. Oxford University Press, 2008.
- 3 Stovner LJ, Hagen K, Jensen R, Katsarava Z, Lipton RB, Scher AI, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007;27:193-210.
- 4 Lipton RB, Bigal M, Diamond M, Freitag F, Reed ML, Stewart WF, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;68:343-9.
- 5 Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754-62.
- 6 Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine- revised report of an EFNS task force. *Eur J Neurol* 2009;16:968-81.
- 7 Antonaci F, Dumitrescu C, De Cillis I, Allena M. A review of current European guidelines for migraine. *J Headache Pain* 2010;11:13-9.
- 8 Mathew N, Kurman R, Perez F. Drug induced refractory headache—clinical

- features and management. *Headache* 1990;30:634-8.
- 9 Linde K, Rosnagel K. propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;2:CD003225.
 - 10 Reveix Herault L, Cardona A, Ospina E, Carrillo P. Effectiveness of flunarizine in the prophylaxis of migraine: a meta-analytical review of the literature. *Revista de Neurologia* 2003;36:907-12.
 - 11 Schrader H, Stovner L, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomized, placebo controlled, crossover study. *BMJ* 2001;322:1-5.
 - 12 Trovnik E, Stovner L, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003;289:65-9.
 - 13 Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. *Arch Neurol* 1979;36:695-9.
 - 14 Moja L, Cusi C, Sterzi R, Canepari C. Selective serotonin re-uptake inhibitors (SSRI) for preventing migraine and tension-type headaches. *Cochrane Database Syst Rev* 2005;3:CD002919.
 - 15 Ozyalcin S, Talu G, Kiziltan E, Yucel B, Ertas M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005;45:144-52.
 - 16 Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. *Neurology* 1994;44:647-51.
 - 17 Mulleners WM, Chronicle EP. Anticonvulsants in migraine prophylaxis: a Cochrane review. *Cephalalgia* 2008;28:585-97.
 - 18 Silberstein SD, Neto W, Schmitt J, Jacobs D. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004;61:490-5.
 - 19 Lipton RB, Gobel H, Einhaupl, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004;63:2240-4.
 - 20 Sandor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* 2005;64:713-5.
 - 21 Schoener J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis—a randomized controlled trial. *Neurology* 1998;50:65-9.
 - 22 Peikert A, Wilimzig C, Kohne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996;16:257-63.
 - 23 Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane Database Syst Rev* 2004;1:CD002286.
 - 24 Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine—a randomized double-blind, placebo-controlled study. *Cephalalgia* 2004;24:838-43.
 - 25 Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGrèy RE, Lipton RB, et al. Onabotulinumtoxin A for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010;30:804-14.

CORRECTIONS AND CLARIFICATIONS

Role of brain imaging in early parkinsonism

In this Rational Imaging article by David P Breen and colleagues (*BMJ* 2011;342:d638, print publication 26 February, pp 495-8) we made a mistake when putting together the images for figure 1. This resulted in the scans being published the wrong way round. The top scan is in fact from the patient with Parkinson's disease, and the bottom scan is from the patient with drug induced parkinsonism.

Obituary: Carys Margaret Bannister

This obituary by Jaleel Miyan (*BMJ* 2010;341:c7238, print publication 1 January 2011, p 51) refers to Carys Bannister as the "first lady neurosurgeon in the UK." It seems that she almost certainly was not. Diana Beck (1902-56) was appointed consultant neurosurgeon at the Middlesex Hospital in 1947, having previously worked at the Frenchay Hospital in Bristol (see www.ncbi.nlm.nih.gov/pubmed/18425021). Beck was probably the female neurosurgeon alluded to by Bannister in the full, online version of the obituary: "As the first 'lady brain surgeon' in the UK (though she herself always said there was one before her who practised during the second world war years but was not fully qualified), Cary received a lot of media attention ..." The parenthetical part was cut from the print version to save space.

Screening for early detection of lung cancer

An editing error occurred in the eighth paragraph of this Observations column by Douglas Kamerow (*BMJ* 2010;341:c6544, print publication 20 November 2010, p 1080). With reference to the US National Cancer Institute's termination of its national lung screening trial, we should have retained Kamerow's original wording: "The study applied only to heavy (30 pack years or more) smokers [not "heavy (30 or more packs a year) smokers"] aged 55 or older."

The rules of retraction

In this Research and Ethics feature article by Melanie Newman (*BMJ* 2010;341:c6985, print publication 11 December 2010, pp 1246-8), Jon Jureidini and Leemon McHenry were quoted extensively but were not acknowledged with a supporting reference. The following reference should have been included: Jureidini J, McHenry L. Conflicted medical journals and the failure of trust. *Accountability in Research* [forthcoming].

Is the NHS only a means of delivering healthcare?

In this letter the email address of the author, Gareth Forbes, was missing an important full point (*BMJ* 2011;342:d983, print publication 19 February, p 397). His correct email address is therefore gareth.forbes@nhs.net (not garethforbes@nhs.net, as published).