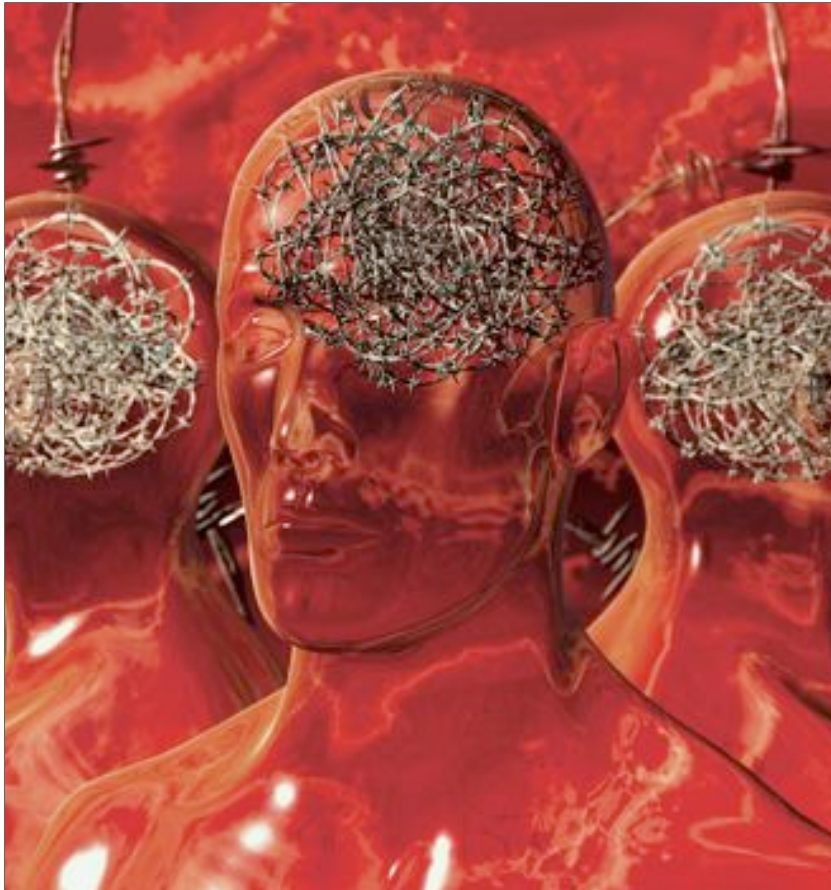


Guide to properties and efficacy of drugs used in migraine

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SPL



It is essential to devise an individualised treatment plan in the management of migraine. Our Drug review considers the properties and efficacy of the various drugs used in treatment and prevention, followed by an analysis of prescription data and sources of further information.

Migraine is a disabling condition that is very common, affecting one in five women and 1 in 13 men in the UK. Prevalence varies with age, peaking at 30 to 40 years and falling in the late 40s.¹ It is episodic and unpredictable and, in addition to having a significant quality-of-life impact on the individual, it also affects their friends, family and work colleagues.^{1,2} It is ranked by the WHO as number 19 among all disease worldwide causing disability.³ The burden to the individual can be dramatically and significantly reduced by finding an effective and flexible acute treatment option and the consideration of a range of preventive strategies.^{2,4}

Diagnosis of migraine

There is no test for migraine, which may or may not be associated with an aura. It is diagnosed by the his-

tory, which takes time to elicit, and sinister causes need to be excluded.⁴ The framework for diagnosis is the International Headache Society (IHS) classification updated in 2004.³ The diagnostic features of the important headaches are shown in Table 1, adapted from the IHS classification.³

Migraine is a high-impact headache. Patients who present with an episodic high-impact headache have migraine or probable migraine.⁵

Aura affects about 6 per cent of migraine sufferers and may be visual (3.3 per cent), sensorimotor (1.2 per cent) or both (1.3 per cent). It lasts from 5 to 60 minutes and resolves completely.¹ Aura may occur in isolation or may be followed with a very mild headache. This tends to occur in the more mature patient, often peri- or postmenopausal women.



CPD questions available for this article. See page 41

The Migraine In Primary Care Advisors (MIPCA) have developed an algorithm that can facilitate the initial assessment of the patient and assist in making the correct working diagnosis. If you get the diagnosis right, then you will get the treatment right. This can be accessed via their website.⁶

Diagnosing chronic migraine

In clinical practice chronic headache remains a diagnostic and management challenge. A revision of the IHS classification in 2006 has endeavoured to reflect this.^{3,7} Chronic migraine and medication-overuse headache are part of the spectrum of chronic headache seen in both primary and secondary care as well as in specialist headache centres, requiring an often complex strategy to support patients in reducing headache days and restoring an episodic headache profile.

Pathophysiology

It is postulated that the aura is caused by a 'cortical spreading depression'.⁸ Activation of the trigeminovascular system leads to dilatation of cranial blood vessels and the throbbing headache. The release of vasoactive neurotransmitter peptides, including substance P, neurokinin A and calcitonin gene-related peptide (CGRP), is thought to lead to a sterile neurogenic inflammation.⁹ The pain process is initiated with activation of primary afferent neurones, with transmission of the pain signal through second-order axons via the trigeminal nucleus to central pain processing areas, including the thalamus, limbic system and neocortex.¹⁰⁻¹²

There is increased cerebral blood volume and reduced blood flow during an attack demonstrated using modern imaging techniques.

Decision making - engaging the patient

When asked, 86 per cent of patients rate complete relief of head pain with no recurrence as important or very important. Rapid onset of relief is important to 83 per cent, no adverse events to 79 per cent and relief of associated symptoms to 76 per cent.²

It is essential to offer flexibility and individualised care to each patient in order to find the treatment mix that works for them.⁴ Up to 21 per cent lapse from care,⁸ so engaging the patient is crucial in ensuring that triggers are understood and managed, and acute treatments are used early enough to maximise benefit^{13,14} and minimise impact on the individual.

Realistic expectations are crucial in developing an understanding of the best way forward.⁴ Using impact questionnaires such as the Headache Impact Test (HIT) and the Migraine Disability Assessment

(MIDAS) can assist the clinician and patient in agreeing an individualised treatment plan that meets the needs of the patient.⁶

Nondrug strategies - diet and lifestyle

'Triggers' are frequently mentioned by patients attending the headache clinic, but I often find it more useful to think about their headache threshold. I encourage people to reflect on factors in their life that have the potential to have a positive effect by pushing their headache threshold up, or recognise factors that may have a negative effect and push their headache threshold down, with each downward nudge making a headache episode inevitable. Understanding personal 'triggers' is essential to reduce the total number of migraine attacks experienced.¹³ Strategies and options vary from person to person and from attack to attack (see Table 2).¹³

Encourage every headache sufferer to put themselves first at least once every day, and if life gets busy, then to ask for help and support from those around them.

Acute treatment

Simple analgesia

Migraine is an inflammatory process associated with gastric stasis. Simple analgesia with or without an antiemetic is effective in treating some migraine attacks.¹⁵ Simple analgesics should be taken as soon as the aura, premonitory phase or headache starts. Headache response, defined as pain going from moderate or severe to mild or none two hours after treatment, after using simple or combination analgesics ranges from 39 to 77 per cent, with an average rate of 60 per cent.¹⁵ The mean pain-free rate (reduction of pain from moderate to severe to no pain two hours

	Migraine with or without aura	Tension-type headache	Cluster headache	Medication-overuse headache
<i>Aura</i>	yes	no	no	no
<i>Headache duration</i>	4-72 hours	30 minutes to 7 days	15-180 minutes	some or all of the day
<i>Frequency</i>	episodic, variable	1-15 days per month, variable	1 on alternate days to 8 per day, often for 7 days to 1 year when episodic	daily >15 days each month
<i>Laterality</i>	unilateral	bilateral	unilateral	unilateral/bilateral
<i>Character of pain</i>	pulsating	pressing/tightening	knife-like, severe, excruciating	pressing/tightening/pulsating
<i>Severity of pain</i>	moderate/severe	mild/moderate	severe/very severe	mild/moderate/severe
<i>Aggravated by movement</i>	yes, need to be still	no	no	no
<i>Eased by movement</i>	no	no	yes, tend to be restless	no
<i>Nausea +/- vomiting</i>	yes	no	no	no
<i>Photophobia/phonophobia</i>	yes	no	no	no
<i>Red watery eye</i>	no	no	yes	no
<i>Watery or blocked nose</i>	no	no	yes	no

Table 1. Important headache types and their diagnostic features (adapted from IHS classification)³

after treatment) is 24 per cent (see Table 3). Pain free is the more robust result and best reflects patients' expectations.²

Translating this research data to clinical practice is challenging because every patient is an individual and how he or she responds to any particular drug will vary, often from attack to attack. They will need a strategy that they can apply that best meets their needs according to the symptoms they are experiencing.⁶

The British Association for the Study of Headache (BASH) guidelines⁴ suggest using aspirin 600-900mg or ibuprofen 400-600mg in buffered solution or orodispersible formulations early, before they are inhibited by gastric stasis. If unsuccessful, alternate agents include tolfenamic acid rapid release (Clotam Rapid) 200mg, naproxen 750-825mg and diclofenac potassium (Voltarol Rapid) 50-100mg with a prokinetic antiemetic to promote gastric emptying such as metoclopramide 10mg or domperidone 20mg. MigraMax (lysine aspirin and metoclopramide sachets) and Paramax (paracetamol and metoclopramide sachets) are both suitable soluble alternatives in a ready-made combination.

If nausea and vomiting appear early or prevent the use of oral medication, diclofenac suppositories 100mg and domperidone suppositories (Motilium) 30mg could be used.

Triptans

Triptans have selective agonist activity at serotonin receptor sites.⁸ These sites within the dura, trigeminal nucleus, the brainstem and the meningeal, dural, cerebral or pial vessels are implicated in the pathogenesis of the migraine attack. Serotonin 1B receptors are not exclusively located on cranial vessels and, as such, may be the reason for some of the side-effects experienced when triptans are taken.⁸

Early treatment of the attack – within one hour of the headache starting – before cutaneous allodynia (pain resulting from a stimulus that does not normally elicit a painful response) develops maximises the chances of successful treatment.¹⁶ The use of stratified care (71 per cent headache response) is more effective and less costly than stepped care (41 per cent response).¹⁶ Stratified care means the patient uses the most aggressive therapy first line for a severe attack rather than stepped care, where a simple analgesic with or without an antiemetic is followed by a triptan. In this situation, early treatment and, on occasion, polypharmacy improves efficacy and reduces headache recurrence.¹⁶

A meta-analysis of 53 triptan trials¹⁷ suggests that when compared to sumatriptan 100mg tablets:

- rizatriptan (Maxalt) 10mg shows better efficacy and consistency and similar tolerability
- eletriptan (Relpax) 80mg shows better efficacy, similar consistency and lower tolerability
- almotriptan (Almogran) 12.5mg shows similar efficacy at two hours but better sustained pain-free response, consistency and tolerability
- sumatriptan 25mg, naratriptan (Naramig) 2.5mg and eletriptan 20mg show lower efficacy but better tolerability
- zolmitriptan (Zomig) 2.5mg and 5mg, eletriptan 40mg and rizatriptan 5mg show very similar results.

Interpreting this information is always difficult as, in trials, patients treat moderate to severe pain but better results are achieved treating mild pain (the latter reflecting clinical practice). The patient wants to be in control of what medication they take and when they take it, which seems to improve outcomes.^{14,16} As a clinician, time should be spent trying alternative triptans (see Table 4) and combinations with NSAIDs with or without an antiemetic until a mix that best meets the individual's need is found.⁴

Triptans should be taken as the headache starts, not when the premonitory symptoms or aura starts. The dose can only be repeated if the headache clears completely and then recurs. They should not be used with uncontrolled hypertension or in anyone with a history of cardiovascular or cerebrovascular disease.

Sumatriptan nasal spray (Imigran) can be used in the 12- to 17-year age group. No triptans are recommended under the age of 12 years; they have, however, been used in specialist centres after careful discussion with the parents and appropriate informed decision-making.

Migraine prophylaxis

Current published evidence^{4,13,18} suggests that preventive medication should be used if the impact on quality of life is high despite acute treatment. Preventive medication may also be used in instances where there is failure of, or contraindication to, acute medication, or troublesome side-effects arising from its use.

Preventive medication may also be used in cases of special circumstances, *eg* hemiplegic migraine, very frequent headache (over two per week) or increasing attacks over time, and if there is patient preference despite effective acute medication.¹⁹

Chronic migraine and medication-overuse headache

It has been shown that stopping acute medication and starting preventive medication produced an improve-

Diet

- eat regularly
 - ideally every 4 hours in the day
 - try not to fast for longer than 12 hours overnight
 - be aware that travel, weekend lie-in, change in shifts and social functions can push your headache threshold down
- avoid known food triggers
- avoid processed sugars and junk foods as much as possible
 - think about low glycaemic index if possible
- hydration
 - 2 litres of water every day
 - reduce caffeine intake as much as possible
 - avoid fizzy drinks as much as possible
 - make extra effort when travelling, weekend lie-in, long shifts, social functions

Stress

- take regular exercise
- plan in advance if a busy day or week is expected
- maintain a regular sleep pattern
- modify your work environment if possible
 - work posture
 - work station
 - lighting
 - regular breaks
- at times of hormonal change, control other 'triggers'

Table 2. Recommended lifestyle and diet changes in the reduction of migraine attacks

ment in 80 per cent of patients after two months,²⁰ and a similar strategy resulted in 70 per cent of patients having episodic headache at one year.²¹

These data, along with other published research, has formed the basis of the strategy adopted at the headache clinic in York. If there is overuse of acute medication we encourage patients to avoid all such medication for at least six weeks, sometimes longer, and discuss with them the use of an appropriate preventive medication to support them during this process.

Using preventive medication

When using preventive drugs, patients should be started at the lowest dose. This should be titrated upwards slowly until a therapeutic effect develops, the maximum dose for that drug is achieved or side-effects are intolerable. Patients should also use the drug for a suitable duration, ideally three months at any dose, and at an adequate dose, which can be titrated down again once control is achieved.

The patient should be involved in the decision-making, such as the consideration of risks and benefits, side-effects, risks of pregnancy (and the need for effective contraception) and realistic expectations (preventive treatment does not stop all attacks and acute treatment will still be needed). A time frame for stopping treatment should be agreed at the start, and comorbidity should be discussed and considered when choosing a preventive drug.

Drugs recommended for use include beta-blockers, TCAs and antiepileptic drugs (AEDs). For options and dose ranges, see Table 5.

Topiramate (Topamax), an AED licensed for migraine prophylaxis, has been shown in three trials²²⁻²⁵ (with propranolol as an active control) to be effective in reducing mean monthly migraine frequency, monthly migraine days and monthly migraine duration at a dose of 50mg twice daily. Topiramate has also been shown to reduce the number of days that acute rescue medication is taken.

In a pooled analysis of MIGR-001, MIGR-002 and MIGR-003 a wide range of adverse events were documented but rarely led to withdrawal.²⁶ The most common was paraesthesia (described as mild to moderate in 50 per cent) with only 8 per cent withdrawing.

Other side-effects include fatigue (15 per cent, withdrawal in 4.7 per cent), anorexia (15 per cent, withdrawal in 4.7 per cent), nausea (13 per cent, withdrawal in 2.3 per cent) and much less commonly, but potentially more problematic, difficulty with memory (6.7 per cent, withdrawal in 2.6 per cent), difficulty with concentration (6 per cent, withdrawal in 1.3 per cent), mood problems (6 per cent, withdrawal in 1.3 per cent) and language problems (6.5 per cent, withdrawal in 1.6 per cent). It is the only preventive drug associated with weight loss as a side-effect (9.1 per cent, withdrawal in 1 per cent).

Side-effects can be reduced by starting at the lowest possible dose, 15mg (using the Sprinkle), and increasing the dose by 15mg every two weeks, as a split dose. The initial target dose is 50mg twice daily, but patients may experience symptom improvement at lower doses. If side-effects develop, step back down to the previous best-tolerated dose.

Topiramate is a liver enzyme inducer and increases the metabolism of oestrogen and progestogen. The dose of topiramate recommended for migraine prevention is 100mg, and has the potential to affect the contraceptive efficacy of combined hormonal contraception, progesterone-only pills and implants, but does not appear to reduce the efficacy of progestogen-only injectables and the levonorgestrel-IUS (Mirena).²⁷

This needs careful discussion and consideration with the patient so that an appropriate informed decision is made and reflects current Faculty of Family Planning guidelines.

Pizotifen, verapamil and SSRIs have not been shown, in large clinical trials, to be of benefit in migraine prevention, or efficacy was compromised by safety concerns.^{4,6}

Methysergide (Deseril) is an effective drug but is best reserved for secondary and tertiary centres due to the risk of retroperitoneal fibrosis.⁴

Venlafaxine A small study of 60 patients taking venlafaxine 75mg and 150mg compared to placebo used a variety of measures to evaluate response including number of headache attacks, pain score, duration of attacks and amount of analgesics used, impact on function and patient satisfaction. The study showed an improvement in the number of headache attacks for the venlafaxine 150mg group compared to placebo. A global efficacy measure showed that 80 per cent of those taking 75mg and 88 per cent of those taking 150mg rated the treatment as good or very good.²⁸

Feverfew, minerals, vitamins and supplements

Feverfew has been shown in some trials to be effective but dispute over the active ingredient requires more trials to establish its role. Riboflavin (vitamin B₂) has been shown to have a responder rate of 59 per cent (placebo 15 per cent, number needed to treat 2.3).¹⁸ Magnesium has been shown to be effective in two out of three trials, but adverse event rates were high.¹⁸

A trial comparing a compound of riboflavin 400mg, magnesium 300mg and feverfew 100mg with a placebo of riboflavin 25mg showed no difference between active and placebo groups using the measure of a 50 per cent or greater reduction in migraine or reduction in migraine days. Riboflavin was used in the placebo because it changes the colour of urine and this dose was felt to be inactive. However, a very high placebo response suggests that this dose may actually be active and more studies may well be needed.²⁹

Butterbur has been found to be safe and effective in treating adults³⁰ and children.³¹ In adults, 68 per cent experienced a ≥ 50 per cent reduction in attack frequency at four months when taking 75mg twice daily.¹⁸ In a study with children and adolescents, 77 per cent of all patients experienced a reduction in attack frequency of 50 per cent at doses of 25mg twice daily for children aged six to nine years and 50mg twice daily for adolescents aged 10-17 years.³¹

A descriptive review of 16 randomised, double-blind, placebo-controlled trials presented as a poster at the 14th IHS Congress concluded that, on the basis of the available information on reduction of migraine frequency and the number of therapy responders, butterbur is as effective as the first-line migraine prophylaxis agent propranolol and as the AED topiramate. Clinical and postmarketing experience has demonstrated that butterbur is safe as long the pyrrolizidine alkaloids have been removed.³²

Co-enzyme Q10 is an essential element of the mitochondrial electron transport chain. If mitochondrial dysfunction plays a part in migraine genesis, then co-enzyme Q10 could reduce migraine headache. In a small study, 32 patients with migraine with or without aura were given a dose of co-enzyme Q10 of 150mg daily. It was generally well tolerated and 61 per cent had a greater than 50 per cent reduction in the number of migraine days.³³

Current needs and future prospects

Triptans have revolutionised the treatment of migraine for many, but are unsuitable for some due to

Drug name	Headache response at 2 hours*	Pain-free response at 2 hours	Placebo
diclofenac 50mg 100mg	39% 44%		22%
MigraMax, [†] first attack	57%	22%	22% 8%
second attack	43%	24%	24% 11%
effervescent aspirin 1000mg	55%	37%	29% 17%
paracetamol [‡] 1000mg	58%	21%	39% 12%
tolfenamic acid 200mg	77%	31%	29% 15%
ibuprofen fast absorbed 400mg	52%		7%
*patients treated for moderate to severe headache within 6 hours of the headache starting ⁸ [†] aspirin 1620mg and metoclopramide 10mg per sachet ⁸ [‡] patients with severe pain and vomiting excluded			

Table 3. Simple analgesics in treating migraine (adapted from reference 8)

side-effects or lack of efficacy. They are not licensed for patients over the age of 65 years and are contraindicated in those with a history of cerebrovascular or cardiovascular disease.³⁴

Two different, unrelated CGRP-receptor antagonists are able to relieve the symptoms of migraine, indicating that CGRP plays a major role in migraine aetiology.^{35,36} To date olcegepant, a potent iv CGRP

antagonist, and oral telcagepant have been found to be safe, effective and well tolerated.³⁷ These agents have not shown vasoconstrictor or vascular side-effects, giving hope to migraine sufferers unable to find an effective treatment for their migraine attacks with the agents currently available.

Chronic migraine, with or without medication over-use, is another challenging area in the clinical setting

Triptan*	Formulations	Drug interactions*
<i>Almotriptan</i>	12.5mg tablet	<ul style="list-style-type: none"> • avoid St John's wort, increased serotonergic effect • ergot or methysergide, avoid for 24 hours after use • ketoconazole, avoid concomitant use (risk of toxicity)
<i>Eletriptan</i>	20mg, 40mg tablets maximum single dose 80mg	<ul style="list-style-type: none"> • avoid clarithromycin and erythromycin • ergot or methysergide, avoid for 24 hours after use • itraconazole, ketoconazole, avoid concomitant use (risk of toxicity) • indinavir, nelfinavir, avoid concomitant use (risk of toxicity)
<i>Frovatriptan</i>	2.5mg tablet	<ul style="list-style-type: none"> • fluvoxamine, may inhibit metabolism • SSRIs, possible increased serotonergic effect • ergot or methysergide, avoid for 24 hours after use
<i>Naratriptan</i>	2.5mg tablet	<ul style="list-style-type: none"> • no significant drug interactions listed
<i>Rizatriptan</i>	5mg, 10mg tablets 10mg wafer	<ul style="list-style-type: none"> • MAOIs, avoid for 2 weeks after use • moclobemide, avoid for 2 weeks after use (risk of CNS toxicity) • propranolol, use 5mg and avoid within 2 hours of propranolol • ergot or methysergide, avoid for 24 hours after use
<i>Sumatriptan</i>	50mg, 100mg tablets 6mg injection 20mg nasal spray 10mg adolescent nasal spray 50mg, 100mg Radis tablets	<ul style="list-style-type: none"> • increased risk CNS toxicity with citalopram, escitalopram, fluoxetine, fluvoxamine • sertraline, avoid concomitant use • MAOIs, avoid for 2 weeks after use • ergot or methysergide, avoid for 24 hours after use
<i>Zolmitriptan</i>	2.5mg tablet 2.5mg, 5mg orodispersible tablets 5mg nasal spray, maximum single dose 5mg	<ul style="list-style-type: none"> • MAOIs, increased risk of CNS toxicity • moclobemide, reduce dose • fluvoxamine, reduce dose • ergot or methysergide, avoid for 24 hours after use • cimetidine, reduce dose • quinolones, reduce dose zolmitriptan (may inhibit metabolism)
Side-effects are a class effect and vary from drug to drug and from person to person; they include tingling, heat, heaviness, pressure, tightness of any part of the body, flushing, dizziness, weakness, nausea, vomiting.*		
* from <i>BNF</i> , March 2010		

Table 4. Triptan formulations and drug interactions

with limited licensed therapeutic options available. PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) 1 and 2 and an analysis of pooled data show that botulinum neurotoxin type A (Botox) is a safe and effective long-term (>24 weeks) prophylactic treatment for chronic migraine.³⁸ In PREEMPT 2 Botox reduced headache-related disability and as a result improved overall functioning and quality of life.³⁹ It was well tolerated, an important fact as many agents used in prophylaxis are poorly tolerated leading to discontinuation.

In clinical practice patients with chronic migraine and medication overuse present the greatest challenge. A subset analysis of the pooled data showed that Botox is both safe and effective in this cohort of patients with highly significant improvement in several different headache symptom measures, ranging from reduced moderate/severe headache days, migraine/probable migraine days and cumulative headache hours on headache days, with few patients stopping treatment due to adverse events.⁴⁰

Botox is now licensed for use in the 'prophylaxis of headache in adults with chronic migraine (headaches on at least 15 days per month of which at least eight days are with migraine)'. This is a useful addition to the range of options available to headache specialists in primary or secondary care.

Conclusion

The focus is the patient. Flexibility in drugs, drug dosages and alternative strategies gives control back to the patient.

All decisions need to be discussed and negotiated in order to maximise benefit to the individual and facilitate an improvement in the quality of life by reducing the duration and frequency of the migraine attack.

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Action	Dosage	Common side-effects	Cautions and contraindications
<p><i>Beta-blockers</i> action not certain but probably central 60-80% effective¹³ >50% reduction in frequency¹³ no dose correlation</p>	<p>80mg daily to 160mg twice daily propranolol LA: 80-160mg daily atenolol: 25-100mg twice daily metoprolol: 50-100mg twice daily</p>	<p>drowsiness, fatigue, lethargy sleep disorders, nightmares depression, memory disturbance, hallucinations</p>	<p>asthma heart failure peripheral vascular disease depression</p>
<p><i>TCAs*</i> action not certain either inhibit noradrenaline and serotonin re-uptake or are antagonists at serotonin₂ receptors useful if mixed-picture headache, eg TTH, other chronic pain condition, disturbed sleep, co-existing depression</p>	<p>2 hours before bedtime or 12 hours before wanting to get up weekly dose titration to initial target dose of 30mg amitriptyline: 10-150mg daily imipramine: 10-150mg daily nortriptyline: 10-100mg daily dosulepin: 25-150mg daily</p>	<p>dry mouth, metallic taste, constipation dizziness, mental confusion tachycardia, palpitations blurred vision, urinary retention weight gain</p>	<p>recent myocardial infarction heart block cardiac arrhythmia</p>
<p><i>Antiepileptic drugs</i> • <i>sodium valproate*</i> (long acting) mode of action not certain may facilitate GABAergic neurotransmission¹³ enhances GABA activity by inhibiting GABA degradation and stimulating synthesis and release¹³ active metabolites do accumulate in the brain¹³ interacts with central serotonin system and reduces midbrain firing rate of serotonergic neurones¹³</p> <p>• <i>gabapentin*</i></p>	<p>300-1000mg twice daily</p> <p>300mg daily up to 800mg 3 times daily slow dose titration to initial 300mg 3 times daily</p>	<p>weight gain GI symptoms hair loss, transient oedema impaired hepatic function sedation haematological disorders</p> <p>dry mouth GI symptoms peripheral oedema dizziness drowsiness anxiety abnormal gait</p>	<p>caution with systemic lupus monitor liver function tests pregnancy and breast-feeding active liver disease family history of severe hepatic dysfunction porphyria anticonvulsant effect may be antagonised by MAOIs, TCAs, SSRIs increased levels with use of cimetidine</p> <p>avoid abrupt withdrawal history of psychotic illness diabetes mellitus pregnancy breast-feeding convulsive threshold may be lowered by TCAs and SSRIs</p>
<p>*unlicensed indication TTH = tension-type headache</p>			

Table 5. Dosages, side-effects and cautions with preventive migraine drugs

Action	Dosage	Common side-effects	Cautions and contraindications
<ul style="list-style-type: none"> • <i>topiramate</i> modulation of variety of processes leads to a reduction in excitatory neurotransmission and enhanced inhibitory neurotransmission ¹⁵ Na ⁺ channel and carbonic anhydrase inhibition ¹⁵ GABA _A receptor, glutamate receptor, Ca ²⁺ channel and K ⁺ channel modulation ¹⁵	15mg Sprinkles fortnightly dose titration to initial target of 30mg twice daily final target dose 50mg twice daily if side-effects develop step back to previous best-tolerated dose	weight loss GI symptoms paraesthesia hypoaesthesia fatigue dizziness somnolence insomnia impaired memory and concentration mood instability	avoid abrupt withdrawal ensure adequate hydration pregnancy breast-feeding associated with acute myopia with secondary angle-closure glaucoma enhances metabolism of oestrogen enhances metabolism of progestogens, unlikely to have effect at doses below 200mg daily

Table 5. Dosages, side-effects and cautions with preventive migraine drugs (cont.)

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Forum



If you have any issues you would like to air with your colleagues or comments on articles published in *Prescriber*, the Editor would be pleased to receive them and, if appropriate, publish them on our Forum page. Please send your comments to:

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Resources

Guidelines

Diagnosis and management of headache in adults. Guideline 107. Scottish Intercollegiate Guidelines Network. November 2008.

Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. British Association for the Study of Headache. January 2007.

Headache – assessment. NHS Clinical Knowledge Summaries. www.cks.nhs.uk/headache_assessment.

Migraine – management. NHS Clinical Knowledge Summaries. www.cks.nhs.uk/migraine.

Groups and organisations

The British Association for the Study of Headache (BASH) is a group of health professionals with a particular interest in the study, treatment and management of headache. Website: www.bash.org.uk.

The British Pain Society is an organisation for professionals aiming to promote education, training, research and development in all fields of pain. Tel:

020 7269 7840; email: info@britishpainsociety.org; website: www.britishpainsociety.org.

Migraine Action is a charity that funds research and provides information for patients and GPs including leaflets and information packs. Tel: 0116 2758317; website: www.migraine.org.uk.

The Migraine In Primary Care Advisors (MIPCA) is an independent charity consisting of a group of healthcare professionals dedicated to the improvement of headache management in primary care. Tel: 01483 450755; website: www.mipca.org.uk.

The Migraine Trust provides free literature for both patients and healthcare professionals. Tel: 020 7462 6601; email: info@migrainetrust.org; website: www.migrainetrust.org.

Websites

The National Headache Foundation provides information on migraine at www.headaches.org.

Patient UK provides several information leaflets on migraine at www.patient.co.uk.

Prescription review

In 2009, GPs in England wrote 2.2 million prescriptions for acute treatments for migraine at a total cost of £54.6 million. Triptans accounted for 83 per cent of volume and 94 per cent of costs. Of these, sumatriptan remained the most frequently prescribed (46 per cent of prescriptions for a triptan) and accounted for the greatest proportion of spending (38 per cent), followed by rizatriptan and naratriptan (17 per cent of volume and about 20 per cent of costs).

Most sumatriptan was prescribed as the 50mg (53 per cent) and 100mg (26 per cent) tablets. The same was true of zolmitriptan (66 per cent as the plain tablet) whereas the lyophilisate formulation (Maxalt Melt) accounted for 72 per cent of rizatriptan prescribing.

Of the combined simple analgesics, Migralve (paracetamol + buclizine; Complete and Pink tablets) and Paramax (paracetamol + metoclopramide) were

	No. scrips (000s)	Cost (£000s)
almotriptan	65	1602
eletriptan	12	469
frovatriptan	54	1244
naratriptan	221	8238
rizatriptan	303	10 266
sumatriptan	832	19 509
zolmitriptan	312	9999
analgesics plus antiemetics	340	2710
ergotamine tartrate	27	418
tolfenamic acid	9	187

Table 6. Number and cost of prescriptions for acute migraine treatments in England, 2009

most frequently prescribed, each accounting for 30 per cent of prescriptions in this category. Paramax accounted for 41 per cent of costs, about equal to both Migralve formulations. Three-quarters of ergotamine prescribing was as Migril tablets.

CPD: Migraine management

Answer these questions online at Prescriber.co.uk and receive a certificate of completion for your CPD portfolio. Utilise the Learning into Practice form to record how your learning has contributed to your professional development.



1. One of these statements about migraine is false – which is it?

- a. Prevalence peaks after age 50
- b. It affects 1 in 5 women
- c. It affects 1 in 13 men
- d. It is ranked by WHO as 19th among all disease worldwide causing disability

2. Regarding the IHS classification of headache, which one of these statements is false?

- a. Cluster headache typically lasts 15-180 minutes
- b. Migraine is not typically associated with red or watery eyes
- c. The pain of medication-overuse headache may be mild, moderate or severe
- d. The pain of migraine is eased by movement

3. Which one of these statements about migraine is false?

- a. Aura affects about 6 per cent of migraine sufferers
- b. An aura lasts for 5 to 60 minutes
- c. Aura is always followed by headache
- d. Aura tends to occur in more mature patients, such as peri- or postmenopausal women

4. Thinking about the pathophysiology of migraine, which one of these statements is false?

- a. Modern imaging techniques have failed to demonstrate changes in cerebral blood volume and blood flow during an attack
- b. Activation of the trigeminovascular system leads to dilatation of cranial blood vessels and the throbbing headache
- c. Release of vasoactive neurotransmitter peptides is thought to lead to a sterile neurogenic inflammation
- d. Migraine is an inflammatory process associated with gastric stasis

5. One of these statements about patients' expectations of treatment of migraine is false – which one?

- a. 86 per cent of patients rate complete relief of head pain with no recurrence as important or very important
- b. Migraine is so troublesome that only 5 per cent of patients lapse from care
- c. Rapid onset of relief is important to 83 per cent of patients
- d. Flexibility and individualised care should be offered to each patient

6. Which one of these statements about nondrug strategies to treat migraine is false?

- a. They involve avoiding events and situations that lower an individual's threshold for developing headache
- b. Exercise should be avoided

- c. Patients should try not to fast for more than 12 hours overnight
- d. Caffeine intake should be minimised

7. Thinking about using simple or combination analgesics to treat migraine, which one of these statements is false?

- a. Simple analgesics should be taken as soon as the aura, premonitory phase or headache starts
- b. The mean pain-free rate (reduction of pain from moderate or severe to no pain 2 hours after treatment) is the preferred endpoint and averages 24 per cent
- c. Headache response, defined as pain going from moderate or severe to mild or none after 2 hours, averages 60 per cent
- d. Soluble or dispersible formulations of analgesics offer no advantage over plain tablets

8. Which one of these statements about the actions and use of triptans is false?

- a. They have selective agonist activity at serotonin receptor sites but serotonin 1B receptors are not exclusively located on cranial vessels
- b. Stratified care is more effective and less costly than stepped care
- c. They should be taken as the premonitory symptoms or aura start, not when the headache starts
- d. Compared with sumatriptan 100mg tablets, almotriptan 12.5mg shows similar efficacy at 2 hours but better sustained pain-free response, consistency and tolerability

9. In the prevention of migraine, which one of these statements is false?

- a. Very frequent headache is defined as at least 5 episodes per week
- b. Preventive treatment does not stop all attacks and acute treatment will still be needed
- c. A time frame for stopping treatment should be agreed with the patient at the outset
- d. Preventive medication may be indicated if a patient prefers it despite taking effective acute medication

10. Which one of these statements about drugs for preventive treatment of migraine is false?

- a. In clinical trials of topiramate, difficulty with memory and concentration, and mood and language problems, each affected about 6 per cent of patients
- b. No patient will obtain benefit from topiramate at doses below 50mg twice daily
- c. Butterbur reduces migraine frequency in adults and children
- d. Botulinum toxin type A has been shown to improve quality of life in patients with migraine