REVIEW

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Chronic daily headache

Mark W Weatherall

Headache is a relatively neglected neurological disorder. Indeed, many neurologists find outpatient headache management—particularly of chronic daily headache—one of the least engaging parts of their job. The neglect of headache as a research problem has been reversed by the relatively recent emergence of strong programmes in centres such as Copenhagen, London, Philadelphia, New York, Liege and Leiden. Partly as a result of this, the pejorative attitude to headache as a clinical problem is less than it was, but many neurologists are still bemused by the intrusion of headache, both at a local level when headache patients occupy scarce specialist beds, and at a global level where the World Health Organization ranks migraine in the top 20 causes of global disability. This article reviews one of the commonest headache syndromes encountered by neurologists—chronic daily headache.

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The next set of notes comes off the top of the pile. A "post-it" note marks the referral letter. "Dear neurologist [the personal touch is always welcome], I would be very grateful for your assessment of this lady with chronic headaches." A quick glance through the text (at least it isn't a computer printout) throws up the usual phrases: "diagnosed as tension headaches"; "has seen several neurologists"; "tried beta-blockers/amitriptyline/pizotifen without success"; "taking ever increasing amounts of analgesics". Do you recognise this patient? Of course you do—after all, chronic daily headache is very common, with an estimated European prevalence of 1–3%. As many as 1.5 million people in the UK may be suffering daily headaches, and they are consuming extensive health service resources in both primary and secondary care.[1] Does your heart sink?

The first section of this article outlines the initial assessment of the patient with chronic daily headache. Two main patient populations emerge:

- those with episodic primary headache disorders (such as migraine), attacks of which have become steadily more frequent over months or years until they have become continuous
- those with new daily persistent headache—that is, headache which is daily from onset, with or without a pre-existing episodic headache disorder.

I will only briefly touch on the latter, a subject that warrants a review to itself. It is interesting and important to note, however, that it is becoming increasingly clear that many patients with truly intractable headache disorders properly fall into this diagnostic category. Perhaps it is here that surgical interventions such as occipital nerve or deep brain stimulation may find their niche in future.

The second section deals with the importance of recognising and treating medication overuse and other conditions believed to be associated with the transformation of episodic headache disorders into chronic daily headache.

The final section is a brief review of the ever-increasing repertoire of drugs available for prophylactic treatment of what is now called chronic migraine, the commonest cause of chronic daily headache, stressing the principles of choice and deployment of these medications.

Assessment of chronic daily headache

Readers of *Practical Neurology* should not need to be told how to take a good history. They might however need to be reminded of the joy of taking a good headache history, which lies in the combination of the familiar with the idiosyncratic that characterises virtually every consultation. Most headache histories contain something that is odd or striking, and it is those details that enliven what can otherwise be a rather routine set of questions.

Chronic daily headache is a syndrome, not a diagnosis. The commonest causes are listed in table 1. The key issue in establishing a diagnosis is the manner in which the headaches became chronic. As mentioned already, there are two common scenarios: the episodic primary headache disorder, attacks of which have become steadily more frequent over months or years until they have become daily and continuous; and headache which simply starts one day and persists on a daily basis

As many as 1.5 million people in the UK may be suffering daily headaches

TABLE 1 Common causes of chronic daily headache

Primary headache disorders
- Chronic migraine
- Chronic tension-type headache
- Chronic cluster headache
- Chronic paroxysmal hemicrania
- Hemicrania continua
- New daily persistent headache (migrainous and tension-type phenotypes)

Secondary headache disorders
- Medication overuse headache
- Chronic post-traumatic headache
- New daily persistent headache (raised intracranial pressure; low CSF volume; chronic meningitis)

TABLE 2 Proposed criteria for medication overuse headache and chronic migraine (2006)

Medication overuse headache

A. Headache present on ⩾15 days/month

B. Regular overuse for >3 months of one or more acute and/or symptomatic treatment drugs as defined under subforms of 2 below
1. Ergotamine, triptans, opioids or combination analgesics on ⩾10 days/month on a regular basis for >3 months
2. Simple analgesics or any combination or ergotamine, triptans, analgesics or opioids on ⩾15 days/month on a regular basis for >3 months without overuse of any single class alone

C. Headache has developed or markedly worsened during medication overuse

Chronic migraine

A. Headache (tension-type and/or migraine) on ⩾15 days per month for at least 3 months

B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for migraine without aura

C. On ⩾8 days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura
1. Has at least two of (a) to (d)
   (a) unilateral location
   (b) pulsating quality
   (c) moderate or severe intensity
   (d) aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
   and at least one of (a) or (b)
   (a) nausea and/or vomiting
   (b) photophobia and phonophobia
2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above

D. No medication overuse and not attributed to another causative disorder

from onset. In the process of becoming chronic or what is sometimes called "transformed", headaches tend to become increasingly featureless, and it is therefore useful to go back to the beginning and ask patients what their headaches were like when they *first* started. The clear definition and autonomic features of cluster headache and the other trigeminal autonomic cephalalgias, the postural variation of headaches associated with low cerebrospinal fluid volume, and other useful diagnostic pointers can all emerge in this way. Patients are often surprised at this emphasis on what their headaches used to be like, rather than what worries them—which is what they are like now. However clues from the past can suggest the diagnosis of the present, most often revising a diagnosis of tension-type headache to one of migraine, but not infrequently raising the possibility of a rarer primary headache disorder or a secondary cause for the headache.

Over the last few years, an inordinate amount of time has been spent debating and refining the definitions of chronic migraine and medication overuse headache. The most recent, most inclusive proposed criteria seem to accord closely with everyday clinical experience (table 2).[2] Recent "road-testing" of the second edition of the *International classification of headache disorders* and its revisions on patients with chronic daily headache shows that medication overuse headache is the commonest diagnosis, and that most patients with this condition have migraine as their underlying disorder once medication overuse has been dealt with (see below).[3] In other words, once medication overuse has been treated, many patients revert to their previous episodic headache disorder, usually migraine without aura. A proportion, however, continue to have headaches on ⩾15 days a month, thus fulfilling the criteria for chronic migraine.

Recognising and treating medication overuse

Where there is a clear history of an episodic primary headache disorder (whichever variety it is) evolving steadily into a chronic daily headache, the first step in management is to understand the factors that may have driven

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that transformation (table 3). Of these, medication overuse is the commonest and, in many cases, the easiest to treat. It alters headache frequency, reduces the effectiveness of prophylactic medication, can change the headache phenotype and even the biology of the disease. It may also complicate the investigation and diagnosis of new daily persistent headache. Interestingly, only those with a history of a primary headache disorder are at risk of developing chronic daily headache from regular analgesic intake.[4] A hint of the mechanism comes from 18-FDG-PET studies of patients with medication overuse headache, which show hypometabolism of the thalami, orbitofrontal cortices, anterior cingulate gyri, insula and ventral striatum, and right inferior parietal lobule—all areas known to be involved in pain processing in many chronic pain disorders. Three weeks after medication withdrawal all these changes resolve except those of the orbitofrontal cortices, which undergo further metabolic decrease, a change previously seen in drug dependency states.[5]

TABLE 3 Factors driving transformation of a primary headache disorder into chronic daily headache

Definite
Medication overuse
Excess caffeine intake
Probable
Psychological comorbidity (anxiety, depression)
Sleep disturbances
Possible
Physical comorbidity (hypertension, hypothyroidism, etc)
Stressful life events
Head injury
Obesity

Myths

There are a number of myths about medication overuse which are prevalent even among neurologists, and which need to be debunked:

- The first is that medication overuse is only a problem with ergots, triptans or opiates. Not true! There is plenty of convincing evidence that overuse of simple analgesics and non-steroidal anti-inflammatories can also drive chronic headaches, as can frequent intake of caffeine (another effective acute headache treatment).[6]
- The second is that medication withdrawal doesn't work. Not true! It does work, and in many cases works fantastically well. Trials of medication withdrawal in outpatients show that one third of patients experience a significant improvement in their headaches, one third a modest improvement, and only one third do not experience any improvement whatsoever.[7] It is extremely unusual for someone to be worse after a period of 4–6 weeks of medication withdrawal, though it is common for patients to experience a transient worsening of their background pain, particularly if coming off opiates.
- Which brings us to the third myth: medication withdrawal can't be done effectively on an outpatient basis. Not true! It can be achieved in most cases. This is a matter of necessity—there are few centres in the UK, and elsewhere, that have the capacity to admit patients for medication withdrawal on more than a very occasional basis—but it is also a matter of fact. It is of course important to identify patients for whom outpatient withdrawal is inadvisable (table 4). For patients with "low medical needs" (that is, no previous attempts at detoxification, no significant comorbidity, and not taking opiates, benzodiazepines or barbiturates), there is no difference in outcome between simple advice to discontinue medication, and structured outpatient or inpatient regimes.[8]

How to withdraw medication

Having decided on the necessity, suitability and feasibility of medication withdrawal, how does one go about it?

- The first step is to decide whether a patient is overusing any medication; the

TABLE 4 Potential exclusion criteria for outpatient withdrawal of overused headache medication

- Severe dehydration, nausea or vomiting
- Use of strong opiates, barbiturates, tranquilisers
- Significant psychiatric comorbidities, particularly where there is a possibility of these conditions being worsened by medication withdrawal
- Significant medical comorbidity (eg, uncontrolled hypertension, severe ischaemic heart disease, etc)
- Previous failure of outpatient withdrawal

Most patients who overuse analgesics will admit that they don't work, or at least not very well

International Headache Society's criteria set ⩾10 days/month for ergots, triptans, opiates and combination medications, and ⩾15 days/month for simple analgesics.[9]

- Identify which medications are being overused.
- Explain the rationale for medication withdrawal.
- Emphasise the generally positive results of medication withdrawal.
- Warn patients they may experience a transient worsening of their headaches.
- Also warn them about nausea, and advise them to avoid dehydration.
- If withdrawing from weak opiates, warn patients about agitation and insomnia.
- Provide prescription for antiemetics; consider a short course of regular clonidine (eg, 25 μg tds, oral) to reduce sympathetic overactivity induced by opiate withdrawal, and/or chlorpromazine (12.5–25 mg prn daily, oral) to reduce agitation or insomnia.
- Ask patients to keep a simple daily headache diary (examples of both successful and unsuccessful medication withdrawal are given in figs 1 and 2).
- Arrange review (clinic/telephone/email/letter).
- A useful rule-of-thumb for advising patients at a stage when analgesics are re-introduced, is that they should be used on no more than two days per week.

Common sense suggests that the most important aspects of this approach are the explanation of the rationale and purpose of medication withdrawal, and the review of its success or otherwise at completion. It is also often helpful to draw out the common observation that most patients who overuse analgesics will admit that they don't work, or at least not very well. With explanation, encouragement and the knowledge that their

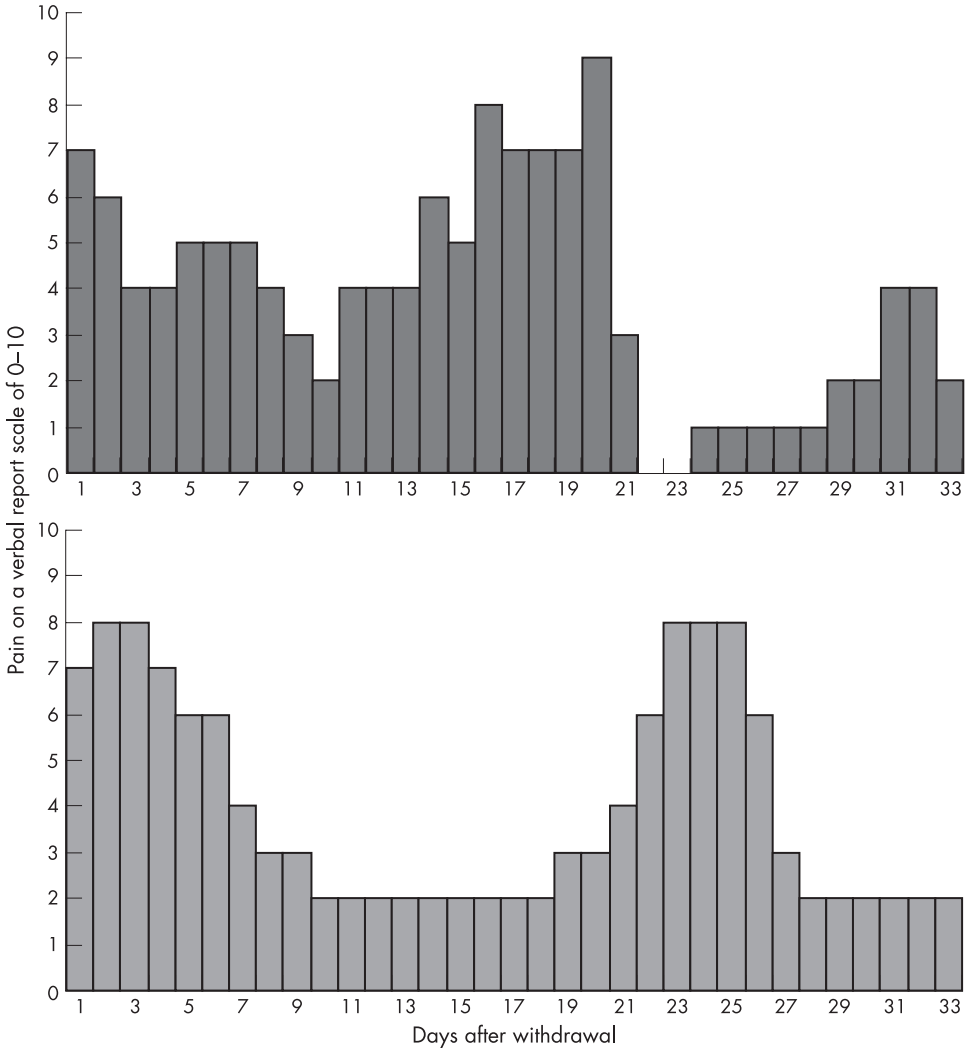

Figure 1
Two headache diaries showing successful medication withdrawal from previous daily headache of 7–10/10 on a verbal report scale. Note fall in background headache level and reappearance of headache-free days, but continuing exacerbations suggesting re-establishment of preceding episodic headache disorder.

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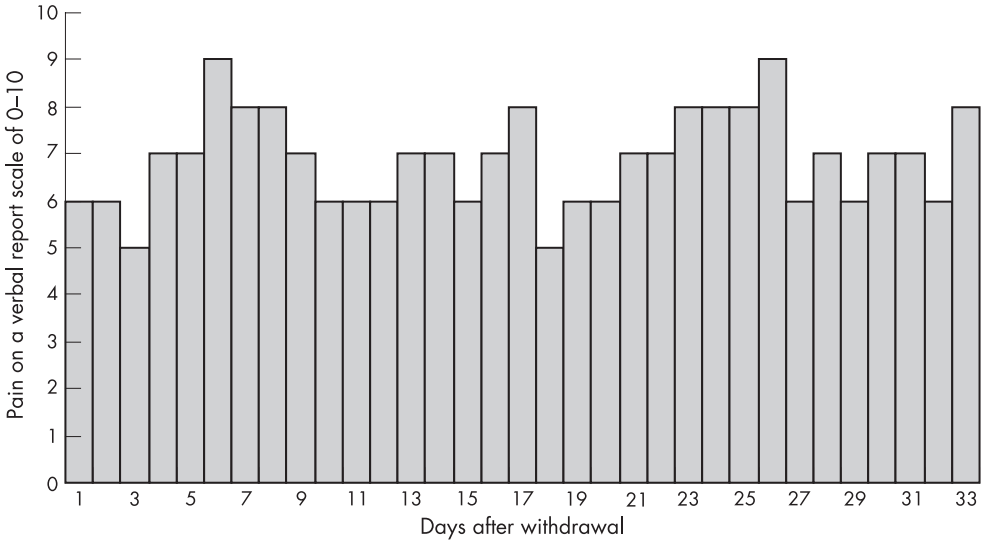

Figure 2
Headache diary showing unsuccessful medication withdrawal.

progress will be reviewed at a set point in the not-too-distant future, most patients are willing to give withdrawal a go. This process of persuasion is a difficult balancing act: how do you convey the necessity of taking this tricky first step in controlling one's headache problem without turning it into a test of moral fibre? The answer is in the art, rather than the science of medicine.

This whole process is made more difficult by certain behaviours and psychological states that may influence an individual's willingness and motivation to endure the process of medication withdrawal,[10] including:

- fear of headache (cephalgiophobia)
- anticipatory anxiety
- obsessional drug-taking behaviours
- psychological drug dependence.

The issues surrounding the review of the success or otherwise of medication withdrawal at completion are primarily logistical. It is rarely appropriate to leave the choice of prophylactic treatment to the patient's primary care physician. The counsel of perfection is to see all patients again in the outpatient clinic, but for many neurologists that may be difficult or impossible. Novel ways of communicating may have to be found. Patients can be asked to send in headache diaries by email or by post; a review of these, often in combination with a brief telephone consultation, may in many cases be sufficient to allow a decision on whether prophylactic treatment is necessary and, if so, which medication should be tried first.

Flexibility is essential. Variations on this "hard-line" withdrawal scheme are often necessary for those who can't or won't withdraw:

- Allow non-steroidals as rescue medication, which is probably the variation least likely to interfere with the long-term success of medication withdrawal, so long as some limits are put on the frequency with which they can be used. Naproxen 500–1000 mg daily is often the non-steroidal of choice. The risk is that patients simply switch one overused analgesic for another.
- Introduce a prophylactic medication immediately. There is some evidence that amitriptyline, sodium valproate, or topiramate may be useful in the context of treating chronic daily headache (as opposed to frequent episodic headaches, which are the type assessed in most trials of headache prophylaxis). The rationale for not doing this routinely is that many patients will not need it after successful medication withdrawal, that prophylactic medication does not work well in the context of medication overuse, and that the completion of medication withdrawal may be complicated by the adverse effects of prophylactic medication.
- Give a short course of high dose oral steroids: a six-day reducing course of prednisolone 60 mg for two days, then 40 mg for two days, then 20 mg for two days reduces pain scores in the first few days of medication withdrawal.[11] It may be argued that this relatively modest (and

Physical and psychological comorbidity are common in patients with chronic headaches

early) benefit outweighs the risks of using steroids in this manner.

- Consider non-pharmacological approaches, particularly where patients take regular analgesics for other chronic pain syndromes; this also applies where you have been able to identify physical (for example, cervicogenic) triggers of migraine or other primary headaches:
  - could back pain be treated effectively with facet joint or epidural injections?
  - would a TENS machine or physiotherapy help?
  - referral to a pain management service can be useful.
  - greater occipital nerve infiltration with lidocaine and depo-medrone is easy to learn, can be done in outpatients, and is often helpful, particularly where point tenderness of the nerve accompanies chronic ipsilateral head pain.[12]

If all else fails, admission to hospital may be the only way forward. The main advantages are:

- parenteral treatments can be used
- nausea and vomiting can be treated with intravenous fluids and anti-emetics
- clonidine and hypnotics can be given as needed
- withdrawal headache can be treated with agents such as intravenous aspirin (1 g maximum tds), intravenous sodium valproate (up to 2 g/day in divided doses or via continuous infusion), or intravenous dihydroergotamine (1 mg tds, up to a cumulative dose of 10 mg, usually over 3–4 days).

All these formulations are available in the UK and Europe, although intravenous aspirin and dihydroergotamine are not generally available outside specialist centres and may have to be requested specially before admission.

The rate of relapse is, unfortunately, high (between one third and one half of patients), being more likely with opiates and simple analgesics than triptans. Most relapses happen within one year.[13]

The bottom line is simple: if you don't deal with medication overuse, attempts at prophylactic treatment of the underlying headache disorder are unlikely to be effective, but if you do, then even previously ineffective prophylactic treatments may work well or not even be needed.[14]

Chronic headaches due to unrecognised "stress"

The patient was a 31-year-old female with no past history of note. Her sister had occasional mild headaches which did not sound particularly migrainous. She lived with her parents, did not smoke and drank alcohol only rarely. She denied other drug use.

When I first saw her she had a six-week history of unremitting headache. This had started as a mild constant headache which shifted from side to side before gradually settling down to the left hand side. This increased in severity over two or three days and she started to become sick and dizzy. Her head started to throb and she found that she was photophobic and mildly phonophobic. When the pain was at its worst she struggled to find words and her speech was slow but there was no dysphasia or stuttering. This all began to settle after about a week but she was left with a residual constant dull pain centred over the left eye, and some pressure around her whole head which she described (rather splendidly) as being "like a pirate's patch over my left eye which has been pulled too tight". On a couple of occasions when the pain was at its worst she experienced blurring of vision; she was generally "dizzy" but without vertigo. There were no autonomic symptoms. There was no postural or diurnal variation to the headache.

There was no past history of headaches apart from some mild headaches following a road traffic accident about 10 years ago. She had been taking various painkillers and was using ibuprofen 400 mg tds, though she felt it had little effect. Examination was normal apart from some tenderness over the left greater occipital nerve.

Phenotypically this was a new daily persistent headache with some migrainous features. Brain imaging was normal and I advised her to stop taking ibuprofen. Six weeks later she had undergone a miraculous recovery and had been headache free for five weeks. Sadly, however, I could not claim any credit, as this recovery clearly coincided with handing in her notice from her previous job, which she had by that stage left altogether. She told me that she had not realised quite how much she had hated it, nor how much stress it was causing her.

Recognising and treating other factors associated with chronic daily headache

Physical and psychological comorbidity are common in patients with chronic headaches, rather better established for medication overuse headache and chronic migraine than for other chronic headache disorders.[15] Whether such cormorbidity causes chronic headaches, or is simply associated with them, is in many cases still unclear; often all we have to go on is anecdotal evidence, as in the case presented in the box. Nonetheless, neurologists dealing with patients with chronic daily headache must expect to find many with:

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TABLE 5 Prophylactic treatments for chronic migraine

	Target daily dose*	Adverse effects	Relative contraindications
Tricyclic antidepressants			
Amitriptyline	100 ± 50 mg	*Common*: drowsiness, dry eyes,	Mania, heart block, urinary retention
Nortriptyline	100 ± 50 mg	dry mouth	
Dothiepin	100 ± 50 mg		
The tricyclics are the first drugs of choice for patients with chronic migraine, and for those with depression, other pain syndromes and many sleep disorders. Small doses can be surprisingly successful, but don't be afraid to push the dose up to "antidepressant" levels. Anecdotally dothiepin may be the least sedating of the commoner drugs.			
Beta-blockers			
Propranolol	80 mg tds	*Common*: fatigue, cold extremities postural	Asthma, depression, diabetes
Atenolol	50 mg bd	hypotension; *rare*: Raynaud's, nightmares,	
Nadolol	80 mg tds	depression, reduced libido	
There is virtually no evidence for the effectiveness of beta-blockers in chronic migraine. They are probably most effective in patients with intermittent severe attacks, or in those with coexisting hypertension or angina. Anecdotally, regular formulations of propranolol are more effective than long acting/slow release formulations.			
Serotonin antagonists			
Pizotifen	3–4.5 mg	*Common*: drowsiness, weight gain	Obesity
Methysergide	4–6 mg	*Common*: leg pains; *rare*: fibrotic reactions	Angina, vascular disease
These might well be the most effective commonly used prophylactic agents, though each is limited by its adverse effect profile; again there is a dearth of evidence in chronic migraine. Pizotifen is well worth reconsidering in patients who have failed previous attempts at prophylaxis, as they will rarely have taken it at anywhere near a maximally effective dose.			
Calcium channel blockers			
Flunarizine	5–10 mg	*Common*: fatigue; *rare*: depression extrapyramidal syndrome	Depression
Flunarizine is highly effective for patients with hemiplegic attacks or prolonged aura, as well as for those with migraine-associated dizziness or vertigo. It is available on a named-patient basis in the UK. Verapamil is omitted from this table because, although it is the drug of choice for cluster headache, it is surprisingly ineffective for migraine; it sometimes has a place for patients with coexisting hypertension or angina who do not tolerate beta-blockers.			
Anti-epileptic drugs			
Sodium valproate	~500–1000 mg	*Common*: drowsiness, ataxia, tremor, weight gain; *rare*: rash	Liver disease, bleeding disorders
Gabapentin	~900–1800 mg	*Common*: drowsiness, ataxia, tremor, weight gain	Liver disease, bleeding disorders
Topiramate	~100–200 mg	*Common*: drowsiness, ataxia, paraesthesias, weight loss; *rare*: kidney stones, acute glaucoma, depression, psychosis	Kidney stones, depression
Gabapentin may be helpful in those with other pain disorders, neuropathic or otherwise. There is some reasonable quality evidence to support the usefulness of valproate and (especially) topiramate in chronic migraine, but there are clearly issues in using these medications in one of the commonest patient groups affected—women of child-bearing age. This is often also the group who are most impressed by topiramate's potential weight reducing properties, however.			
Other options. There are no other prophylactic agents that have been adequately trialled in chronic migraine. By analogy with episodic migraine, monoamine oxidase inhibitors such as moclobemide or phenelzine, which have traditionally been regarded as migraine prophylactics of last resort, though in many cases effective, may be useful, particularly in patients with refractory depression or panic disorders; a strict dietary regime is necessary. Trials of certain ACE inhibitors and angiotension II blockers (lisinopril and candesartan) show modest effectiveness, as do trials of magnesium (pick a formulation (eg citrate) that will be absorbed), riboflavin, and co-enzyme Q10. Trials of botulinum toxin are unconvincing, but those of acupuncture are better, though traditional Chinese needle points don't seem to be any more effective than non-traditional points. Present information on the effectiveness of patent foramen ovale closure is not sufficient to allow it to be recommended for the treatment of any headache disorder. Occipital nerve stimulation is less invasive than deep brain stimulation and may be as effective in patients with intractable migraine (for a working definition of intractability, see the recent statement paper in *Cephalalgia*.[17]) Trials are ongoing at several centres around the world, including the National Hospital for Neurology and Neurosurgery in London.			

*The dose to be reached, if tolerated, before conceding treatment failure.

PRACTICE POINTS

- Chronic daily headache is common and debilitating, with a prevalence of 1–3%.
- The vast majority of these patients can be helped with proper management.
- Medication overuse is common and needs to be treated before a definitive diagnosis can be made and appropriate treatment instituted; *any* painkillers can cause medication overuse headache.
- Medication overuse can often be treated successfully on an outpatient basis.
- Physical and psychological comorbidities are common in patients with chronic daily headache and may require treatment before the headache disorder can be successfully managed.
- When using prophylactic treatment for headache disorders, start with a low dose and gradually titrate up to a "decent daily dose" which should be maintained for 6–8 weeks (provided there are no limiting adverse effects) before abandoning treatment as ineffective
- If at first you don't succeed, persevere.
- Programmes to reduce the burden of headache can only start by the neurological community taking a more active and proactive approach to the management of debilitating primary headache disorders.

- psychological problems such as depression, generalised anxiety disorder, panic disorder, and bipolar disorder
- sleep disorders such as obstructive sleep apnoea, sleep-disordered breathing, periodic limb movement disorder, sleep phase disorders, insomnia, and hypersomnia
- other chronic pain disorders, often musculoskeletal or arthritic
- other physical disorders, such as hypothyroidism, functioning and non-functioning pituitary tumours, and hypertension.

Management of some of these associated conditions may complicate the management of the headache disorder, for example by initiating or perpetuating medication overuse. On the other hand, treatment of a physical, psychological or metabolic disorder may improve the headache problem (sometimes leading to the diagnosis of a secondary headache disorder) or may at least remove certain restrictions on treatment options for the headache. Although neurologists cannot be expected to deal with all (or even any) of these issues, they should be able to recognise them and direct the patient to the appropriate services as necessary. To do this effectively it is necessary to develop local networks of expertise, which might include (among others) neuroradiologists, neurosurgeons, ear nose and throat surgeons, dentists or maxillofacial surgeons, ophthalmologists, cardiologists, endocrinologists, obstetricians and gynaecologists, sleep specialists, pain specialists and anaesthetists, psychiatrists, psychologists and behavioural therapists, physiotherapists, pharmacists, dieticians, and nurse specialists.

Prophylactic treatments for chronic migraine

So now you have treated your patient's medication overuse headache successfully, but he or she continues to have chronic daily headache. Let us assume now that the phenotype is migrainous, because most chronic headache is migraine. Despite this, however, most of the research on prophylactic treatments has concentrated on episodic migraine. Very few preventative agents used for chronic migraine have been examined in well-designed trials. Table 5 summarises the current armamentarium, with some notes on efficacy, likelihood and nature of adverse effects, and some treatment tips.

The principles of the choice and use of prophylaxis are rather similar to the recommended principles of epilepsy management, one of the main differences being that (unlike epilepsy) it is not sensible to encourage the patient to expect to become completely headache-free, as this rarely happens. Normal practice is to use monotherapy, selecting from first-line treatments according to tolerability and patient choice, starting low to minimise the risk of adverse effects, and then steadily increasing the dose until either a desired improvement is achieved, or the patient experiences intolerable adverse effects, or a decent dose has been tried without success. Following the failure of first-line monotherapy, a systematic search through the second- and third-line alternatives should be undertaken. As Richard Lipton and four other giants of headache research point out in their article "Why headache treatment fails", persistence can be very rewarding.[16] Once a correct diagnosis has been reached and exacerbating factors have been addressed, the commonest reason for treatment failure is not using sufficiently high

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doses over realistic time periods (at least 6–8 weeks).

Another significant difference from epilepsy therapy is that combinations of prophylactic treatments are much less commonly used, though this is an area in which we may see increasing scientific and clinical contributions in future.

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