The diagnosis and treatment of chronic migraine

Mark W. Weatherall

Ther Adv Chronic Dis
2015, Vol. 6(3) 115–123
DOI: 10.1177/2040622315579627

***Abstract*:** Migraine is the most common disabling brain disorder. Chronic migraine, a condition characterized by the experience of migrainous headache on at least 15 days per month, is highly disabling. Patients with chronic migraine present to primary care, are often referred for management to secondary care, and make up a large proportion of patients in specialist headache clinics. Many patients with chronic migraine also have medication overuse, defined as using a compound analgesic, opioid, triptan or ergot derivative on at least 10 days per month. All doctors will encounter patients with chronic headaches. A basic working knowledge of the common primary headaches, and a rational manner of approaching the patient with these conditions, allows a specific diagnosis of chronic migraine to be made quickly and safely, and by making this diagnosis one opens up a substantial number of acute and preventive treatment options. This article discusses the current state of management of chronic migraine.

Keywords: chronic migraine, headache, medication overuse headache, migraine

Correspondence to:
Mark W. Weatherall, PhD FRCP Ed
Princess Margaret Migraine Clinic, Imperial College NHS Healthcare Trust, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK
mark.weatherall@imperial.ac.uk

Introduction

Migraine is a common disabling brain disorder. Headache accounts for 4.4% of all consultations in general practice [Tepper *et al.* 2004; Kernick *et al.* 2008b], approximately 5% of all medical admissions to hospital [Weatherall, 2006], and approximately 20% of neurology outpatient consultations [Stone *et al.* 2010]. Migraine affects over 20% of people at some point in their lives; epidemiological studies have shown that 4.5% of the population of Western Europe has headache on at least 15 days per month [Welch and Goadsby, 2002]; global studies suggest that approximately 1% of the world's population may have chronic migraine [Natoli *et al.* 2010]. Chronic migraine imposes a substantial economic burden on society [Buse *et al.* 2012]. Migraine is so common that, even though for many people it is no more than an inconvenience, the cumulative burden of the disorder caused it to rank in the top 40 conditions causing worldwide disability according to the World Health Organization's 2012 global burden of disease figures, above all other neurological disorders other than stroke, meningitis and epilepsy; in the United Kingdom it ranks third behind stroke and the dementias, causing the loss of 230,000 DALYs (Disability-Adjusted Life Years) annually [World Health Organization, 2012].

Chronic migraine is the term that the International Classification of Headache Disorders (ICHD) uses to describe patients with frequent headaches, believed to be biologically migrainous [Headache Classification Committee of the International Headache Society, 2013] The meaning of the term 'chronic migraine' has evolved over the last two decades, as it has steadily replaced earlier terminology such as 'chronic daily headache' and 'transformed migraine' [Olesen *et al.* 2006; Zeeberg *et al.* 2009; Goadsby *et al.* 2010]. There is ongoing debate about whether a further subdivision of the diagnosis should be created to specify patients who are refractory to treatment [Martelletti *et al.* 2014]. The broader acceptance of the concept that migraine can be a chronic condition has led to increasing interest in the pathophysiology, epidemiology, and treatment of this condition [Diener *et al.* 2012].

Patients with chronic headaches have in the past experienced the adverse effects of lack of education about headaches, and therapeutic nihilism.

Box 1. Secondary causes for new daily persistent headache phenotype.

Thunderclap headache
Subarachnoid haemorrhage
Cerebral venous sinus thrombosis (CVST)
Reversible cerebral vasoconstriction syndrome
Carotid/vertebral artery dissection
Pituitary apoplexy
Intracerebral haemorrhage/haematoma
Hypertensive encephalopathy
Idiopathic thunderclap haemorrhage (Call_Fleming syndrome)
Persistent worsening headaches
Raised cerebrospinal fluid (CSF) pressure (tumour, abscess, CVST, idiopathic intracranial hypertension)
Low CSF volume (post-lumbar puncture, spontaneous CSF leak)
Meningitis (acute/chronic)
Hypoxia/hypercapnia
Substance abuse/withdrawal
Systemic inflammatory conditions, including temporal arteritis

There is now no excuse for either of these factors to impact upon the management of these patients. As this article will show, it is almost always possible to make a specific diagnosis in patients with chronic migraine, and by making this diagnosis one opens up a substantial number of treatment options.

Diagnosis of chronic migraine

Recognize the pattern

When assessing a patient with chronic headaches (that is, by definition, headaches on at least 15 days per month), it is important from the outset to ascertain how the headaches originally developed. There are two typical patterns. In one set of cases, patients with a pre-existing primary headache disorder (usually, but not exclusively migraine) have ever-increasing attacks until they reach a stage where they do not recover headache freedom in between, a pattern originally called 'transformed migraine' [Mathew, 1987; Silberstein *et al.* 1996]. In the other set of cases, patients start to have a headache one day, and it simply never goes away. This is a syndrome that goes under the name 'new daily persistent headache' (NDPH) [Goadsby and Boes, 2002], and is an important pattern to recognize because it is within this set of headaches that many of the serious causes lie, including those conditions which may present with a thunderclap headache (Box 1). After investigation, however, many cases of new daily persistent headache do not have an underlying cause, and are essentially chronic versions of the more familiar episodic headache disorders [Robbins *et al.* 2010].

Patients may be surprised that you want to know about events that happened in the past (sometimes some years previously) and what their headaches used to be like, but because chronic headaches often become steadily more featureless over time, establishing the original phenotype can be crucial in making an accurate diagnosis, without which treatment is unlikely to be successful.

Recognize the disorder

Migraine is the commonest cause of recurrent, severe headache. It is experienced at some point by over 20% of women and over 10% men. The tendency to suffer from migraine has a genetic basis, but individual attacks may be triggered by internal or external influences, or simply come by themselves for no apparent reason. The name 'migraine' originally comes from the Greek word *hemicrania*, meaning 'half of the head', representing one of the most striking features of the condition: that in many cases pain only affects one half of the head. Equally commonly, however, pain is felt bilaterally, at the front or the back of the head, more rarely in the face, and rarer still in the body ('migrainous corpalgia'). The pain is generally throbbing in nature, and typically made worse by any form of movement or even modest exertion. The majority of migraine attacks are severe or at least moderately so.

Box 2. International Classification of Headache Disorders diagnostic criteria for migraine.

(1) At least five attacks fulfilling criteria (2)–(4)
(2) Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
(3) Headache has at least two of the following four characteristics:
  (a) unilateral location
  (b) pulsating quality
  (c) moderate or severe pain intensity
  (d) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
(4) During headache at least one of the following:
  (a) nausea and/or vomiting
  (b) photophobia and phonophobia
(5) Not better accounted for by another ICHD-3 diagnosis.

The pain of migraine is typically accompanied by other features such as nausea, dizziness, extreme sensitivity to lights, noises, and smells, lack of appetite, disturbances of bowel function, and so on. The typical constellation of symptoms experienced by migraine sufferers is reflected in the ICHD criteria for the diagnosis of migraine (Box 2). It should be remembered that these criteria were originally designed for the purpose of ensuring coherent patient populations for research in headache disorders, and that not everyone's migraine has 'read the textbook'.

Only about 20% of migraine sufferers experience *aura*, usually (but not invariably) before the headache starts. Most aura is visual, consisting of a combination of positive visual phenomena (floaters, flashes of light, moving or expanding zig-zag patterns, and so on) and negative phenomena (loss of vision causing blind spots). Many sufferers also experience sensory aura, consisting of tingling and numbness, often spreading over the hand, arm, face, lips and tongue on one side of the body. Weakness, dysphasia, and other aura symptoms are rare.

Between 10% and 20% of migraineurs experience premonitory symptoms up to 48 h before their migraines [Giffin *et al.* 2003]. These may include fatigue or abnormal bursts of energy, neck stiffness, yawning and frequent urination. Particular areas of the brain have now been identified that are active during the premonitory phase [Maniyar *et al.* 2014]. A higher proportion experience a postdrome during which they may experience grumbling headache, a bruised feeling in the head, fatigue and nausea, and a continuing sensitivity to lights, noises, smells and movement.

Take a detailed history

Accurate history taking is vitally important in the diagnosis of migraine. It is important to give patients time to describe their attacks fully (it may well be the first time that anyone has listened to them talk about their pain), and also to clarify the history with specific questions aimed at filling out the gaps in what the patient has told you spontaneously. The diagnosis of migraine lies in the history, and that the purpose of examination is primarily to look for other problems that may be exacerbating an underlying tendency to migraine. This may in most cases be restricted to fundoscopy, inspection and palpation of the head and neck structures, and a brief screening cardiovascular and neurological examination, unless, on the basis of the history, serious intracranial or systemic pathology is suspected.

As mentioned above it is useful to begin with questions about the *pattern* of the pain, including when, and how headaches begin; whether they are continuous, episodic or (as is often the case in chronic migraine) continuous with episodic exacerbations; the duration of episodes or exacerbations; and if there are any triggers or exacerbating factors. After this questions can be asked about the *nature* of the pain, such as its location, character, severity (using a verbal report scale of 0–10, where 0 is no pain and 10 is the worst imaginable). Then the presence of *associated symptoms* that accompany the pain should be ascertained; these include symptoms that precede attacks suggesting a prodrome or aura, such as excessive tiredness or energy, yawning, excessive urination, neck stiffness, vertigo, visual or sensory disturbances; symptoms that accompany attacks such as nausea, sensitivity to lights, noises, smells, touch, or movement; and symptoms suggesting alternative primary or secondary headache disorders

such as eye watering, conjunctival injection, nasal congestion, ptosis, eyelid oedema, sweating, agitation, fever, neck stiffness or rash.

It is then useful to ascertain what *treatments*, current and previous, have been tried, and at what point these treatments are taken. Patients should be asked to bring a list of medications tried in the past, including doses, and be asked why these treatments were abandoned (ineffective/side effects). The use of alternative or complementary therapies should also be sought.

Finally, it is also important to ask questions about the patient's previous *medical history* (including questions about depression, anxiety and sleep disorders), current nonheadache medications, allergies, *family history* (especially of headache), and *social history* (including occupation, smoking status, and levels of alcohol and caffeine consumption). It can also be helpful to ask about markers of migraine such as recurrent abdominal pain, motion sickness or a greater than expected tendency to hangovers. It is useful to know if the patient has seen other medical or nonmedical practitioners about their headaches, what conclusions were reached, and what investigations if any were carried out.

While superficially there seems to be a lot of information required, it is almost invariably the case that patients will volunteer much of this information without being specifically asked, and it usually does not take too much time to fill out the gaps if a structured approach to the history taking is followed. If there is uncertainty, then encouraging the patient to keep a *headache diary* can be very useful.

Investigate appropriately

Decisions on investigation of patients with chronic migraine are driven by two highly prevalent cultural myths: that headaches are commonly due to brain tumours; and that in modern medicine diagnoses can only be made on the basis of an abnormal scan or blood test result. With regard to the former, evidence shows that when a diagnosis of migraine can be made on clinical grounds, the chances of the patient having a brain tumour are 0.045% [Kernick *et al.* 2008a]; no investigation is indicated, therefore, not least because there is a 1–2% chance of picking up an incidental intracranial abnormality which may cause anxiety, or even have an adverse influence on life insurance applications. Imaging should be reserved for situations when clinical assessment suggests that the probability of an underlying tumour has exceeded 1%; examples include the finding of papilloedema on fundoscopy, headache with fixed abnormal neurological signs, headaches associated with new onset seizures or significant alterations in consciousness, memory or coordination, or headaches in patients with a history of cancer elsewhere in the body. In such cases magnetic resonance imaging is the modality of choice. Other investigations such as blood tests or cerebrospinal fluid analysis are only indicated in cases of diagnostic uncertainty, most typically when patients present with the NDPH phenotype.

Make a diagnosis

In cases of chronic headaches, the phenotype is often not clear. Useful *a priori* assumptions are that primary headache disorders (particularly migraine) present more commonly to doctors than do secondary headaches, and that it is unusual for patients to have to seek medical opinions about mild headaches, such as tension-type headache. Asking about the patient's original headaches often elicits the story of an episodic headache disorder with migrainous features, evolving into a chronic disorder (often but not invariably driven by overuse of painkillers or caffeine [Bigal *et al.* 2008], psychological comorbities such as anxiety or depression, physical conditions such as sleep apnoea or significant life events), and in such cases chronic migraine is the most likely diagnosis. In some cases it may not be possible to make a definitive diagnosis (the ICHD recognizes this, including categories of 'probable migraine' and 'unclassifiable' headaches); nonetheless if the patient is experiencing chronic headaches sufficiently severe to interfere with normal everyday activities, then in the absence of an alternative cogent primary or secondary headache diagnosis, it is reasonable to treat them on the basis that chronic migraine is the most likely cause.

It is important to try to make a diagnosis, even it is only a presumptive one; explaining this to the patient, accompanied by reassurance that there is no serious underlying cause, is the first step in treatment, and may in some cases be the only intervention required.

Treatment of chronic migraine

There are three broad approaches to treating chronic migraine: lifestyle and trigger management,

acute treatments (i.e. those taken during attacks or exacerbations of chronic pain), and preventive treatments (medication or other interventions designed to reduce the tendency to have attacks). While many patients find that lifestyle adjustments such as regularizing meals and sleep can reduce the frequency of their attacks, some form of medication or other treatment is almost invariably necessary in patients with chronic migraine. The National Institute for Health and Care Excellence (NICE) have recently published guidance on the diagnosis and treatment of migraine, and further consensus guidelines have been published by the British Association for the Study of Headache, the American Headache Society and American Academy of Neurology, and the European Headache Federation [Loder *et al.* 2012].

Lifestyle modification and trigger reduction

When patients have chronic severe headaches, it can be difficult to recognize specific triggers. Paradoxically it is often the case that as chronic headaches start to improve with treatment, triggers become more obvious. Regularity of regimen with regard to meals, hydration, sleep and stress is always helpful in reducing the tendency to migraines; recognizing that this is helpful is straightforward, but actually making the requisite changes in a modern busy life may be more difficult.

Many patients with chronic migraine will have other problems that exacerbate their tendency to headaches: these include depression, anxiety, other pain syndromes such as fibromyalgia, localized pain in head and neck structures, and conditions that create 'metabolic' strain such as sleep apnoea or postural orthostatic tachycardia syndrome. Proper management of these is necessary to maximize the effect of any other migraine treatments. It is particularly important to recognize and manage medication overuse (including caffeine overuse) as failure to do so will render most attempts at preventive treatment ineffective [Lipton *et al.* 2003].

Acute headache treatments

Patients with chronic migraine often find it difficult to know when to take acute treatments. Both patients and physicians may be concerned about the possibility of medication overuse, and in the early stages of management it may be preferable to avoid acute painkillers altogether. Once a stage is reached where there are clear 'good days and bad days', or a situation when there is a background headache with clearly defined exacerbations, then acute treatment can be reintroduced. The usual principles apply: attacks should be treated early, when the pain is still mild; effective doses should be used, treatments being titrated steadily up to the maximum tolerated dose before being abandoned as ineffective; associated symptoms such as nausea should also be treated; and an appropriate route of delivery should be chosen (various medications can be given by nasal spray or via a suppository). If simple analgesics are not effective, then triptans should be used and opiates avoided if possible [Ferrari *et al.* 2002]. Potential acute treatments are listed in Box 3. Strict limits should be set on the frequency with which acute treatments are used to avoid worsening the situation through medication overuse. Recently there has been interest in noninvasive stimulation techniques such as transcranial magnetic stimulation [Lipton *et al.* 2010] and vagal nerve stimulation [Goadsby *et al.* 2014]. Early data suggest that these may be as effective as standard analgesics in the acute treatment of migraine, and that prolonged use may start to reduce headache frequency.

Preventive treatment

Preventive treatment is usually considered when headache frequency or severity increases to a point when it is significantly interfering with work, school or social life. For patients with chronic migraine this is invariably the case, and some form of preventive medication or other intervention is almost universally indicated. Evidence from the American Migraine Prevalance and Prevention study shows, however, that as many as 40% of those patients who might benefit from preventive treatment are never offered it [Lipton *et al.* 2007].

Numerous medications have been shown to be effective in the preventive treatment of migraine. Not all of these are licensed for this purpose in the United Kingdom. The choice of treatment can be influenced to varying degrees by the pattern of headaches, patient comorbidity, tolerability, teratogenicity, potential side effects, ease of use and patient choice. Preventive treatments should be commenced at a low dose to minimize the possibility of developing side effects. The dose should be steadily and regularly increased until the medication works, intolerable side effects occur or a

Box 3. Acute migraine treatments.

Paracetamol 1 g
Aspirin 900–1200 mg
Ibuprofen 400–800 mg
Naproxen 250–500 mg
Triptans
- Sumatriptan 50–100 mg orally, 10–20 mg nasal, 6 mg subcutaneously
- Almotriptan 12.5 mg
- Eletriptan 40–80 mg
- Frovatriptan 2.5 mg
- Naratriptan 2.5–5 mg
- Rizatriptan 5–10 mg, s/l melt
- Zolmitriptan 5–10 mg orally, s/l melt, 5 mg nasal

Combinations
- Sumatriptan 50 mg and naproxen 250–500 mg
- (all of the above are taken alone or with domperidone 10 mg orally, or an alternative antiemetic)

Single-pulse transcranial magnetic stimulation
Vagal nerve stimulation

s/l, sublingual.

maximum dose is reached, at which point it can be concluded that the medication does not work for that individual patient. Adherence should be closely monitored, as levels are known to be low [Blumenfeld *et al.* 2013; Hepp *et al.* 2014]. At this point another preventive treatment can be tried. If preventive treatment works well, it should be continued for a few months before weaning the dose down. In many cases this process can be achieved without headache frequency suddenly worsening again.

Specific trials in patients with chronic migraine are sparse, and in many cases the evidence for the use of standard preventive medications has to be extrapolated from studies in patients with high-frequency episodic migraine. Whilst NICE has recently recommended topiramate as the first-line preventive (on the basis that this medication has the most extensive high-quality clinical trial evidence on which to base the decision), most headache specialists continue to start with other older medications, probably of equivalent efficacy and certainly better tolerated, such as tricyclics (amitriptyline [Dodick *et al.* 2009], nortriptiline or dosulepin), β blockers (propranolol [Linde and Rossnagel, 2004], atenolol, nadolol or metoprolol). If these do not work then anticonvulsants such as topiramate [Diener *et al.* 2007; Silberstein *et al.* 2007; Mulleners *et al.* 2015] or sodium valproate [Yurekli *et al.* 2008; Mulleners *et al.* 2015] can be considered. The calcium channel blocker flunarizine may be helpful [Diener *et al.* 2002], and anecdotally is said to be the drug of choice for patients with prolonged aura, hemiplegic attack or prominent vertigo. There is also increasing evidence that angiotensin blockers such as candesartan are useful and well tolerated in migraine prevention [Tronvik *et al.* 2003; Stovner *et al.* 2013]. Details of dose regimes are given in Table 1.

If first- or second-line preventives fail, the patient should be referred to a specialist headache clinic for reevaluation, and consideration of nonpharmacological interventions such as greater occipital nerve blocks (case series suggest this may be useful in reducing headache frequency and severity for a limited period in over 50% of patients [Afridi *et al.* 2006], though a recent double-blind randomized controlled trial casts doubt on this [Dilli *et al.* 2014]) or Botox (onabotulinum toxin A; Allergan, Irvine, CA) injections for chronic migraine (two successive sets of injections of 155–195 U in seven areas of the head and neck having been shown to reduce headache days by 50% over 6 months in such patients) [Aurora *et al.* 2011]. Ultimately neurosurgical techniques such as occipital nerve stimulation or deep brain stimulation can be considered for the rare but challenging truly intractable cases [Magis and Schoenen, 2012].

Conclusion

Chronic migraine is an important treatable cause of neurological disability. It is vital to make

Table 1. Preventive headache treatments for chronic migraine.

First line	Starting dose	Target dose
β blockers		
Propranolol	10 mg three times daily	40–80 mg three times daily
Metoprolol	25 mg twice daily	100 mg twice daily
Atenolol	25 mg once daily	100 mg once daily
Angiotensin blockers		
Candesartan	4 mg once daily	12–16 mg once daily
Tricyclics		
Amitriptiline	10 mg *nocte*	75–100 mg *nocte*
Nortriptiline	10 mg *nocte*	75–100 mg *nocte*
Dosulepin	25 mg *nocte*	75–100 mg *nocte*
Second line		
Anticonvulsants		
Topiramate	12.5 mg *nocte*	50–100 mg twice daily
Sodium valproate	200 mg *nocte*	400–800 mg twice daily
Flunarizine	5 mg once daily	5–10 mg once daily
Onabotulinum toxin A (Botox)	155 U (PREEMPT protocol)	
Supplements		
Riboflavin (vitamin B2)	400 mg daily	
Magnesium citrate (or taurate)	600 mg daily	

a diagnosis and ensure that any concomitant medical or psychological conditions are treated in parallel with interventions aimed at reducing the biological tendency to headaches. It is also important to set patients' expectations as to what can be achieved. The tendency to migraine is genetic, and will rise and fall in people's lives; migraine cannot be 'cured' in any sense. It can be managed, however, and often very successfully following the lines outlined in this article.

There are interesting times ahead for the management of chronic migraine. New acute and preventive options should become available over the next 3–6 years, including calcitonin gene-related peptide (CGRP) antagonists and antibodies, and drugs targeted at other serotonin receptor subtypes. In the meantime, however, our existing armamentarium holds plenty of possibilities for clinicians and patients to work together to improve the lives of people with chronic migraine.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The author declares no conflict of interest in preparing this article.

References

Afridi, S., Shields, K., Bhola, R. and Goadsby, P. (2006) Greater occipital nerve injection in primary headache syndromes–prolonged effects from a single injection. *Pain* 122: 126–129.

Aurora, S., Winner, P., Freeman, M., Spierings, E., Heiring, J., DeGryse, R. *et al.* (2011) Onabotulinum toxin a for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache* 51: 1358–1373.

Bigal, M., Serrano, D., Buse, D., Scher, A., Stewart, W. and Lipton, R. (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 48: 1157–1168.

Blumenfeld, A., Bloudek, L., Becker, W., Buse, D., Varon, S., Maglinte, G. *et al.* (2013) Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). *Headache* 53: 644–655.

Buse, D., Manack, A., Serrano, D., Reed, M., Varon, S., Turkel, C. *et al.* (2012). Headache impact of episodic and chronic migraine: results from the American Migraine Prevalence and Prevention study. *Headache* 52: 3–17.

Diener, H., Bussone, G., Van Oene, J., Lahaye, M., Schwalen, S. and Goadsby, P. (2007) Topiramate reduces headache days in chronic migraine: a

randomised, double-blind, placebo-controlled study. *Cephalalgia* 27: 814–823.

Diener, H., Dodick, D., Goadsby, P., Lipton, R., Olesen, J. and Silberstein, S. (2012) Chronic migraine – classification, characteristics, and treatment. *Nat Rev Neurol* 14: 162–171.

Diener, H., Matias-Guiu, J., Hartung, E., Pfaffenrath, V., Ludin, H., Nappi, G. *et al.* (2002) Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 22: 209–221.

Dilli, E., Halker, R., Vargas, B., Hentz, J., Radam, T., Rogers, R. *et al.* (2014) Occipital nerve block for the short-term preventive treatment of migraine: a randomized, double-blinded, placebo-controlled study. *Cephalalgia* 12 December (epub ahead of print).

Dodick, D., Freitag, F., Banks, J., Saper, J., Xiang, J., Rupnow, M. *et al.* (2009) Topiramate versus amitriptyline in migraine prevention: a 26-week, multicentre, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clin Ther* 31: 542–549.

Ferrari, M., Goadsby, P., Roon, K. and Lipton, R. (2002) Triptans (serotonin 5-HT 1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 22: 633–658.

Giffin, N., Ruggiero, L., Lipton, R., Silberstein, S., Tvedskov, J., Olesen, J. *et al.* (2003) Premonitory symptoms in migraine: an electronic diary study. *Neurology* 60: 935–940.

Goadsby, P., Ahmed, F., Tyagi, A. and Weatherall, M. (2010) The changing face of chronic migraine: who to treat, how to treat? *Satellites* 15: 1–4.

Goadsby, P. and Boes, C. (2002) New daily persistent headache. *J Neurol Neurosurg Psychiatry* 72(Suppl. 2): ii6–ii9.

Goadsby, P., Grosberg, B., Mauskop, A., Cady, R. and Simmons, K. (2014) Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. *Cephalalgia* 34: 986–993.

Headache Classification Committee of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 33: 629–808.

Hepp, Z., Dodick, D., Varon, S., Gillard, P., Hansen, R. and Devine, E. (2014) Adherence to oral migraine-preventive medications among people with chronic migraine. *Cephalalgia* 27 August (epub ahead of print).

Kernick, D., Ahmed, F., Bahra, A., Dowson, A., Elrington, G., Fontebasso, M. *et al.* (2008a) Imaging patients with suspected brain tumour. Guidance for primary care. *Br J Gen Pract* 58: 880–885.

Kernick, D., Stapeley, S., Goadsby, P. and Hamilton, W. (2008b) What happens to new-onset headache presenting to primary care? A case-cohort study using electronic primary care records. *Cephalalgia* 28: 1188–1195.

Linde, K. and Rossnagel, K. (2004) Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* (2): CD003225.

Lipton, R., Bigal, M., Diamond, M., Freitag, F., Reed, M. and Stewart, W. (2007) Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 68: 343–349.

Lipton, R., Dodick, D., Silberstein, S., Saper, J., Aurora, S., Pearlman, S. *et al.* (2010) Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. *Lancet Neurol* 9: 373–380.

Lipton, R., Silberstein, S., Saper, J., Bigal, M. and Goadsby, P. (2003) Why headache treatment fails. *Neurology* 60: 1064–1070.

Loder, E., Burch, R. and Rizzoli, P. (2012) The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache* 52: 930–945.

Magis, D. and Schoenen, J. (2012) Advances and challenges in neurostimulation for headaches. *Lancet Neurol* 11: 708–719.

Maniyar, F., Sprenger, T., Monteith, T., Schankin, C. and Goadsby, P. (2014) Brain activations in the premonitory phase of nitroglycerin triggered migraine attacks. *Brain* 137: 232–242.

Martelletti, P., Katsarava, Z., Lampl, C., Magis, D., Bendtsen, L., Negro, A. *et al.* (2014) Refractory chronic migraine: a consensus statement on clinical definition from the European Headache Federation. *J Headache Pain* 28: 15–47.

Mathew, N. (1987) Transformed or evolutional migraine. *Headache* 27: 305–306.

Mulleners, W., McCrory, D. and Linde, M. (2015) Antiepileptics in migraine prophylaxis: an updated review. *Cephalalgia* 35: 51–62.

Natoli, J., Manack, A., Dean, B., Butler, Q., Turkel, C., Stovner, L. *et al.* (2010) Global prevalence of chronic migraine: a systematic review. *Cephalalgia* 30: 599–609.

Olesen, J., Bousser, M., Diener, H., Dodick, D., First, M., Goadsby, P. *et al.* (2006) New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 26: 742–746.

Robbins, M., Grosberg, B., Napchan, U., Crystal, S. and Lipton, R. (2010) Clinical and prognostic subforms of new daily persistent headache. *Neurology* 74: 1358–1364.

Silberstein, S., Lipton, R. and Sliwinski, M. (1996) Classification of daily and near-daily headaches: field trial of revised IHS criteria. *Neurology* 47: 871–875.

Silberstein, S., Lipton, R., Dodick, D., Freitag, F., Ramadan, N., Mathew, N. *et al.* (2007) Efficacy and safety of topiramate for the treatment of chronic migraine: a randomised, double-blind, placebo-controlled trial. *Headache* 47: 170–180.

Stone, J., Carson, A., Duncan, R., Roberts, R., Warlow, C., Hibberd, C. *et al.* (2010) Who is referred to neurology clinics? – The diagnoses made in 3781 new patients. *Clin Neurol Neurosurg* 112: 747–751.

Stovner, L., Linde, M., Gravdahl, G., Tronvik, E., Aamodt, A., Sand, T. *et al.* (2013). A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. *Cephalalgia* 34: 523–532.

Tepper, S., Dahlöf, C., Dowson, A., Newman, L., Mansbach, H., Jones, M. *et al.* (2004) Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. *Headache* 44: 856–864.

Tronvik, E., Stovner, L., Helde, G., Sand, T. and Bovim, G. (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 289: 65–69.

Weatherall, M. (2006) Acute neurology in a twenty-first century district general hospital. *J R Coll Physicians Edinb* 36: 196–200.

Welch, K. and Goadsby, P. (2002) Chronic daily headache: nosology and pathophysiology. *Curr Opin Neurol* 15: 287–295.

World Health Organization (2012) *WHO Global Health Estimates: DALYs, 2000–2012*. Available at: http://www.who.int/healthinfo/global_burden_disease/en/ (accessed January 2015).

Yurekli, V., Akhan, G., Kutluhan, S., Uzar, E., Koyuncuoglu, H. and Gultekin, F. (2008) The effect of sodium valproate on chronic daily headache and its subtypes. *J Headache Pain* 9: 37–41.

Zeeberg, P., Olesen, J. and Jensen, R. (2009) Medication overuse headache and chronic migraine in a specialized headache centre: field-testing proposed new appendix criteria. *Cephalalgia* 29: 214–220.