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Supplement

July 2025

Focus on headache

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SUPPLEMENT
FOCUS ON HEADACHE
JULY 2025

ISSN 1443-430X

SYDNEY OFFICE
Suite 503, Level 3
116 Military Road
Neutral Bay NSW 2089

POSTAL ADDRESS
PO Box 1473, Neutral Bay NSW 2089

TELEPHONE (02) 9908 8577
FACSIMILE (02) 9475 0645

EMAIL
Editorial enquiries
reception@medicinetoday.com.au
Production enquiries
mariamarmora@medicinetoday.com.au
Advertising sales enquiries
prueanderson@medicinetoday.com.au
General enquiries
reception@medicinetoday.com.au

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MedicineToday
THE PEER REVIEWED JOURNAL OF CLINICAL PRACTICE

FOREWORD FROM THE SUPPLEMENT EDITORS

Headache is one of the most common and complex presentations in general practice. This *Focus on headache* supplement brings together expert advice to support GPs in navigating the wide spectrum of headache disorders – from the everyday to the potentially life-threatening.

It begins with a practical approach to investigating headache in primary care, before moving to a contemporary update on migraine management, including the latest treatment strategies. Chronic daily headache and the nuances of episodic migraine in women are explored in depth, highlighting diagnostic and therapeutic challenges. The supplement also covers unusual primary headache syndromes, the crucial recognition of thunderclap headache and the often-overlooked issue of medication overuse headache.

Together, these articles aim to sharpen diagnostic confidence and guide effective, evidence-based care for patients with headache.

Professor Richard J. Stark AM, MB BS, FRACP, FANZAN, MACLM
Neurologist in the Neurology Department, The Alfred Hospital; and Adjunct Clinical Professor in the Department of Neuroscience, Monash University, Melbourne, Vic.

Dr Shuli Cheng MB BS, FRACP
Neurologist in the Neurology Department, The Alfred Hospital, Melbourne, Vic.

Dr Jason C. Ray MB BS, FRACP, PhD
Neurologist in the Department of Neurology, Alfred Health and the Department of Neurology, Austin Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne, Vic.

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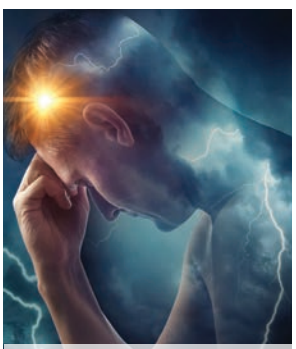

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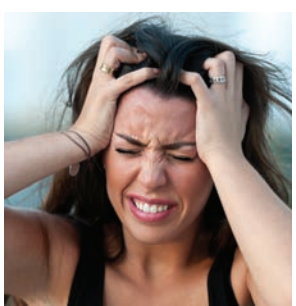

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Headache
Investigating the cause

RICHARD J. STARK AM, MB BS, FRACP, FANZAN, MACLM

Headaches are a frequent presenting complaint in primary care settings. Diagnoses are primarily clinical, with some specific indications for further investigation. This article provides specialist advice and allows GPs to review their existing knowledge and expertise on this common presentation.

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Most patients with headache have one of the primary headache disorders, such as migraine, but sometimes headache can be the presenting feature of serious neurological disease. Thoughtful and judicious use of investigations is required to diagnose patients with secondary headache, without submitting those with primary headache to unnecessary tests. It is vital to have a strategy in mind when seeing patients with headache as indiscriminate investigation is likely to be unproductive and wasteful.

Useful strategies when diagnosing patients with headache are to:

- classify headaches according to tempo (i.e. the time course of the evolution of symptoms) to help clarify the likely causes and thus determine which investigations, if any, should be pursued
- have in mind a list of red flags that would trigger specific investigative paths.

Some of the investigations referred to in this article may be impractical for a GP to undertake. In these situations, referral of patients to an emergency department or for specialist care is appropriate.

KEY POINTS

- Most patients presenting with chronic or recurrent headache will have one of the primary headache disorders; therefore, investigations are unlikely to be abnormal.
- GPs will be familiar with the usual presentation of the common primary headaches. These headaches can often be diagnosed without further investigation.
- Headaches occurring with new, abrupt onset or with relentless progression are likely to be caused by specific pathology and patients should be referred for appropriate testing and treatment.
- In most cases requiring brain imaging, MRI is preferable over CT. GPs should consider the practical difficulties for patients with regards to cost, access and availability.
- The mnemonic 'SNOOP-4' (systemic, neurological, onset [sudden or after 50 years of age], pattern change, precipitated by Valsalva manoeuvre, postural aggravation, papilloedema) is a useful checklist of red flag conditions in patients presenting with headache.

A sound understanding of the usual presentation of the common primary headaches is vital (Box 1). Often, these headaches can be diagnosed without the need for special tests. However, sometimes limited investigation is required, if only to fully reassure both the patient and clinician in the case of atypical presentations.

Fortunately, the time course of most primary headaches is characteristic and distinguishes them from other possibilities.

The pattern of headaches can be regarded as:

- acute headache of instantaneous onset (likened to the snap of one's fingers)
- acute headache developing over minutes to days

MedicineToday 2025; 26(7 Suppl): 2-7
First published in Medicine Today 2023; 24(6): 29-36
Updated July 2025

Professor Stark is a Neurologist in the Neurology Department, The Alfred Hospital, Melbourne; and Adjunct Clinical Professor in the Department of Neuroscience, Monash University, Melbourne, Vic.

1. CAUSES OF PRIMARY HEADACHE

Migraine and related disorders
- Migraine with and without aura
- Migraine equivalents
- Transformed or chronic migraine

Tension-type headache
- Episodic and chronic headache

Cluster and related (trigeminal or autonomic cephalalgias)
- Cluster headache
- Short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome
- Hemicrania continua
- Episodic paroxysmal hemicrania

Neuralgias
- Trigeminal and glossopharyngeal
- Postherpetic and injury-related neuralgias

Other
- Ice pick pains (idiopathic stabbing headache)
- Benign sex headache and exercise headache

2. CAUSES OF INSTANTANEOUS THUNDERCLAP HEADACHE

- Subarachnoid haemorrhage
- Benign sex or exertional headache
- Reversible cerebral vasoconstriction syndrome
- Pressor responses or sudden hypertension (e.g. phaeochromocytoma, monoamine oxidase inhibitor)
- Expanding aneurysm
- Carotid or vertebral dissection
- Migraine

- subacute headaches developing over days to weeks
- recurrent headaches
- recurrent facial pain
- chronic headaches (more than 15 days per month for more than three months).

Each of these patterns raises a distinct range of diagnostic possibilities and, hence, a particular approach to investigation.

Instantaneous headache

Headache developing instantaneously, likened to the snap of one's fingers, requires urgent action, mainly to avoid missing the diagnosis of subarachnoid haemorrhage. Although some causes are benign, these can only be diagnosed after serious pathology has been excluded (Box 2). More detail on instantaneous (thunderclap) headache is presented in a separate article in this collection.

Subarachnoid haemorrhage

Instantaneous headache must be regarded as a subarachnoid haemorrhage until proven otherwise. In practice, this will often mean referral of any patient with an acute presentation to an emergency department.

Modern imaging (CT or MRI scan of the brain) is usually sensitive at detecting subarachnoid blood if performed within a few days of a subarachnoid haemorrhage (Figure 1). Lumbar puncture may occasionally show a subarachnoid haemorrhage (by revealing blood or chemically confirmed xanthochromia) when the diagnosis is unclear on imaging, but a traumatic tap may confound interpretation. If the patient presents later than a week after the abrupt headache, subarachnoid blood may no longer be apparent and investigation should then focus on a possible source of the haemorrhage.

Modern CT angiography (CTA) or magnetic resonance angiography (MRA) is reasonably sensitive at demonstrating aneurysms (Figure 2) and arteriovenous malformations. If a subarachnoid haemorrhage is confirmed, or is strongly suspected despite negative CTA or MRA, catheter angiography should be performed.

Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) may cause single or recurrent episodes of instantaneous headache. CTA or MRA may show vasospasm, but this may not be apparent immediately; the radiological changes may appear a few days after the initial presentation with headache. Localised ischaemic changes or very focal subarachnoid haemorrhage may be seen in patients with this condition. Some cases of benign orgasmic headache may fit into this category, but usually investigation is normal with this condition. Expanding aneurysms or arterial dissection should be apparent on CTA or MRA.

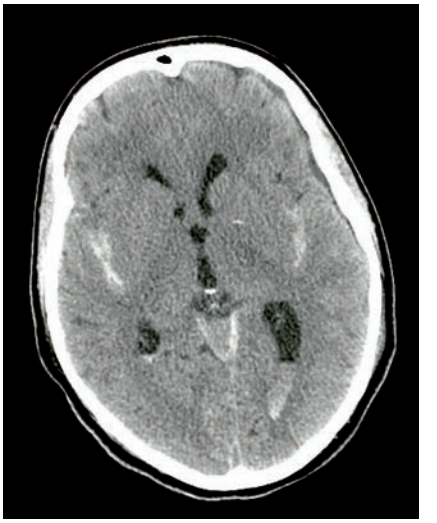


Figure 1. CT scan showing subarachnoid blood in the sylvian fissures and lateral ventricle.

Phaeochromocytoma

Abrupt onset of headache associated with labile or recent elevation of blood pressure would trigger consideration of a phaeochromocytoma. Appropriate biochemical testing should then be undertaken.

Arterial dissection

Sudden onset of focal pain in the posterior neck (vertebral artery), front of the neck or behind the eye (carotid artery) might suggest possible arterial dissection, especially if associated with trauma to the region. The trauma may be severe (such as from major motor accidents) or minor (such as from sharp head turning or chiropractic manipulation). MRA is often very helpful in

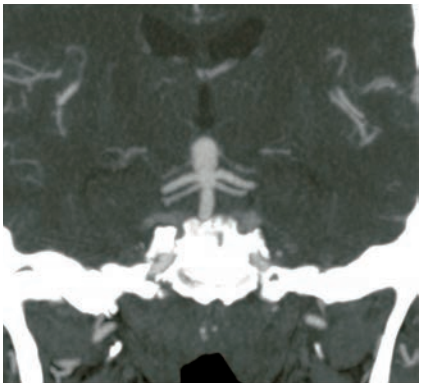


Figure 2. CT angiogram showing an aneurysm at the tip of the basilar artery.

clarifying this diagnosis, but it must include the vessels in the neck (such views are often not included if they are not specifically requested). CTA and catheter angiography may also show such lesions.

Noninstantaneous acute headache

Headaches developing over hours or a day or two should also raise concerns about serious conditions (Box 3). If fever or other indicators of infection are present, meningitis and encephalitis must be excluded.

Meningitis and encephalitis

If bacterial meningitis is a genuine consideration, blood cultures should be taken. Urgent treatment with antibiotics should begin at once, preceding specific investigation that would usually involve brain imaging first and then a lumbar puncture (unless this was contraindicated by the imaging findings).

For possible encephalitis, investigation should include an early MRI scan (Figure 3), a lumbar puncture with a specimen sent for detection of herpes simplex virus by polymerase chain reaction, as well as a routine cell count, culture, biochemistry, and appropriate investigation for less common infectious agents. Treatment with antiviral agents to cover herpes simplex virus infection will usually be started if herpes encephalitis is considered a possibility, pending results of investigations.

3. CAUSES OF NONINSTANTANEOUS ACUTE HEADACHE

- Meningitis or encephalitis
- Systemic infections
- Acute obstructive hydrocephalus
- Reversible cerebral vasoconstriction syndrome
- Pressor responses (e.g. phaeochromocytoma, monoamine oxidase inhibitors)
- Expanding aneurysm
- Carotid or vertebral dissection
- Venous sinus thrombosis
- Low-pressure headache
- Migraine

Systemic infections

GPs will be familiar with acute viral illnesses such as influenza or infectious mononucleosis presenting with headache as a prominent early symptom. Appropriate investigations should be undertaken if these conditions are suspected.

Headache from raised pressure

Urgent brain imaging should always be undertaken in patients with acutely developing headaches, unless the diagnosis is obvious on clinical grounds. Imaging will show a structural mass lesion large enough to cause headache from raised pressure, including hydrocephalus. Venous sinus thrombosis may be missed if the appearances of the venous sinuses are not examined specifically. Therefore, MR or CT venography should be included in the investigation if this condition is suspected.

Low-pressure headache

Headaches developing or changing in nature after a lumbar puncture or epidural injection raise the possibility of low intracranial pressure, especially if aggravated by the upright posture. Occasionally, similar headaches develop spontaneously (e.g. from leakage of cerebrospinal fluid from a nerve root sleeve). This can be a difficult diagnosis to make, but clues would be a postural element to the headache and

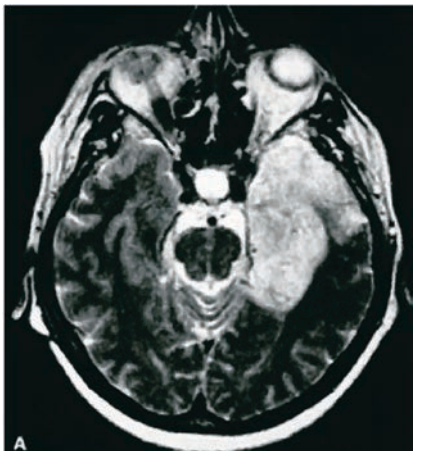


Figure 3. MRI (T2) showing herpes simplex virus encephalitis. The abnormality in this case (white area) involves the medial and anterior temporal lobes predominantly, which is characteristic of herpes simplex virus encephalitis.

some characteristic changes on MRI of the brain including 'sagging' of the brain stem, engorgement of venous sinuses and abnormal enhancement of the dura.

Postlumbar puncture headaches are often treated with a lumbar epidural blood patch, without further investigation, if the clinical presentation is typical. If the diagnosis is in doubt, an MRI scan of the brain (with contrast) may show the characteristic appearance mentioned above.

Subacute headache

Relentlessly progressing headache over days to weeks is suggestive of serious pathology (Box 4). Once again, brain imaging, preferably MRI, is vital to exclude an intracranial space-occupying lesion (Figure 4) or progressive hydrocephalus. If the symptoms or signs are suggestive of raised intracranial pressure (e.g. a history of visual obscurations on rising to standing or papilloedema on examination) but imaging is unremarkable, idiopathic intracranial hypertension (previously termed benign intracranial hypertension) should be considered. This possibility would lead to a lumbar puncture with recording of the cerebrospinal fluid pressure. A lumbar puncture would also be diagnostic in cases of chronic meningitis.

4. CAUSES OF SUBACUTE HEADACHE

- Expanding intracranial lesion
- Progressive hydrocephalus
- Temporal arteritis
- Subacute meningitis (e.g. tuberculosis or cryptococcus, neoplastic meningitis)
- Benign intracranial hypertension
- Low-pressure headache
- Facial or cranial pathology (e.g. sinusitis, Tolosa-Hunt syndrome, glaucoma)

In a patient over 55 years of age with progressive headache, temporal arteritis must be considered and erythrocyte sedimentation rate and C-reactive protein level measured. Temporal artery tenderness should be looked for and temporal artery biopsy should be pursued if the diagnosis seems possible after these preliminary tests.

Headaches may arise from the sinuses, neck, eyes, or temporomandibular joint and dental disorders, but these causes are usually suggested by the history and examination. These possibilities should be pursued with appropriate investigation or referral.

Recurrent headache or facial pain

Most patients with recurrent headache have one of the primary headache disorders (Box 5).

Migraine

Migraine is a diagnosis based on typical clinical features. Criteria have been set out in the *International Classification of Headache Disorders* (ICHD, 3rd edition; Box 6).[1] Migraine is very common and all doctors will have a sound appreciation of the usual features and be attuned to recognising what is atypical. If the history is typical, investigation is usually not required.

Migraine without aura is characterised as a recurrent headache disorder manifesting in attacks lasting four to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity and association with nausea, photophobia or phonophobia.[1]

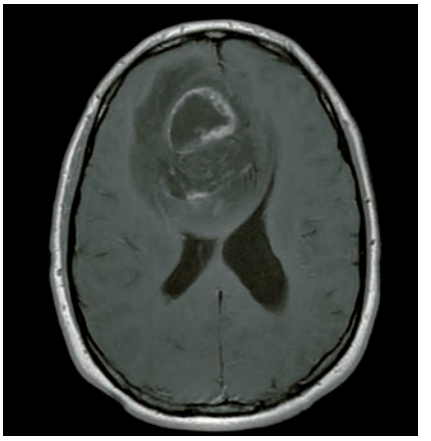


Figure 4. MRI (T1 after gadolinium) showing a very large glioblastoma multiforme. Tumours in the frontal region may produce only subtle focal features, such as changes in behaviour, and may thus become large before being detected. Headache from raised intracranial pressure may be the presenting feature.

Migraine with aura is a recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over five to 20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent. Typical aura consists of visual, sensory or speech symptoms. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility are characteristic.[1]

Generally, focal neurological symptoms would be an indication for imaging the brain, unless typical of migraine aura. The usual visual aura symptoms of scintillating scotoma or fortification spectra are well known, but an understanding of the typical evolution of symptoms of migraine with aura over five to 60 minutes is equally important. A more rapid evolution over seconds to a few minutes would raise suspicion of a focal seizure (and thus a likely structural lesion), whereas an abrupt, almost instantaneous onset might suggest stroke or transient ischaemic attack.

5. CAUSES OF RECURRENT HEADACHE AND FACIAL PAIN

- Migraine
- Cluster headache
- Trigeminal or glossopharyngeal neuralgia
- Benign sex or exercise headache
- Ice pick pains (idiopathic stabbing headache)
- Ice cream headache (the common transient headache that occurs in normal individuals after ingesting frozen food)
- Paroxysmal severe hypertension (e.g. phaeochromocytoma)
- Reversible cerebral vasoconstriction syndrome (recurrent thunderclap headache)
- Episodic tension-type headache

Migraine is typically underdiagnosed in the community. The formal ICHD 3rd edition criteria are difficult to remember for day-to-day diagnostic use and simpler user-friendly diagnostic methods have proved to be almost as reliable as the formal criteria. One such approach is the three question method suggested by Lipton and colleagues.[2] These three questions are:

- in the past three months, has a headache interfered with your activities on at least one day?
- when you have a headache, do you feel nauseated (sick)?
- when you have a headache, does light bother you?

If the answer is yes to two or three of these questions, the diagnosis is highly likely to be migraine.

Cluster headache

Cluster headache has such a characteristic time course that, in most cases, a firm diagnosis can be made with great confidence from the patient's history. The attacks are of severe, strictly unilateral pain that is orbital, supraorbital or temporal, or in any combination of these sites, lasting 15 to 180 minutes and occurring from once every other day to eight times a day. The

6. THE *INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS-3* DIAGNOSTIC CRITERIA FOR MIGRAINE

Classification [A to E]

With aura

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:
- visual
- sensory
- speech and/or language
- motor
- brainstem
- retinal

C. At least three of the following six characteristics:
- at least one aura symptom spreads gradually over five minutes
- two or more aura symptoms occur in succession
- each individual aura symptom lasts five to 60 minutes[1]
- at least one aura symptom is unilateral[2]
- at least one aura symptom is positive[3]
- the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis

Without aura

A. At least five attacks fulfilling criteria B to D

B. Headache attacks lasting two to four hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following characteristics:
- unilateral location
- pulsating quality
- moderate or severe pain intensity
- aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache, at least one of the following:
- nausea and/or vomiting
- photophobia and phonophobia

E. Not attributed to another disorder

Adapted from Headache Classification Subcommittee of the International Headache Society. *The International Classification of Headache Disorders*. 3rd ed. Cephalalgia 2018; 38(Suppl 1): 1-211.[1]

7. CAUSES OF CHRONIC HEADACHES

Primary chronic headaches (may be associated with medication overuse or rebound headache)
- Tension-type headache
- Transformed migraine or chronic migraine
- New daily persistent headache
- Hemicrania continua

Secondary chronic headaches
- Post-traumatic or cervicogenic headache
- Atypical facial pain
- Nonparoxysmal neuralgias (e.g. postherpetic neuralgia)

attacks are associated with one or more of the following, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and eyelid oedema. Most patients are restless or agitated during an attack.[1]

As lesions in the region of the cavernous sinus can sometimes produce a similar clinical picture to cluster headache, most neurologists would now obtain an MRI scan and MRA of the brain in such cases. However, the results are rarely abnormal.

Trigeminal neuralgia

Trigeminal neuralgia is a unilateral disorder characterised by brief electric shock-like pains. They are abrupt in onset and termination, and limited to the distribution of one or more divisions of the trigeminal nerve. Pain is often evoked by trivial stimuli, including washing, shaving, smoking, talking or brushing the teeth (trigger factors), and frequently occurs spontaneously. Small areas in the nasolabial fold and chin may be particularly susceptible to the precipitation of pain (trigger areas). The pain usually remits for variable periods.[1]

Trigeminal neuralgia is often due to compression of the root entry zone of the nerve by a vascular loop. This may be apparent with carefully directed MRI or MRA, which should also detect other less usual causes, such as other lesions compressing the nerve or a plaque of multiple sclerosis in the pons.

Ice pick pains (idiopathic stabbing headache)

Idiopathic stabbing headache is transient and consists of localised stabs of pain in the head. These pains occur spontaneously in the absence of organic disease of underlying structures or of the cranial nerves. This is a relatively common and benign disorder.

Benign sex headache and exertional headache

As subarachnoid haemorrhage may occur during exertion or sexual activity, headache occurring in these contexts must always be taken seriously. Naturally, if many similar events have occurred with no disastrous consequences, subarachnoid haemorrhage is much less likely. However, RCVS is still a concern and appropriate imaging is required.

Chronic headache

There has been much interest in recent years in the concept of chronic daily headache. This is a pattern of headache occurring more than four hours per day for 15 or more days per month and for more than three months. Headaches arising from cervical spine pathology or persistent neuralgic pain after herpes zoster virus infection would fall into this category and are usually easy to recognise. The term chronic daily headache is usually reserved for the primary headaches presenting with this time course (Box 7).

Mild cases often fall into the category of tension-type headache (defined in essence as primary headache without migrainous or other diagnostic features), but most disabling cases have chronic migraine. Chronic migraine is diagnosed when a patient has 15 or more days of headache per month with migraine features on at least eight days. Many patients evolve

from a pattern of episodic typical migraine to a more frequent headache pattern with fewer typical migrainous features. Excessive (e.g. more than 10 days per month) use of acute medications, such as ergotamines, triptans or codeine, may contribute to this transformation.

New daily persistent headache begins over one to three days and then persists, with the patient usually being able to give the precise date of onset. This rare type of headache is notoriously difficult to treat. Hemicrania continua is a rare, strictly unilateral headache that is specifically responsive to indomethacin.

In general, the group of patients with chronic headache is challenging to manage and taking a detailed history is vital. Investigation is usually normal but imaging is undertaken at some stage in most of these patients.

Recognising the red flags

One mnemonic for red flag signs in patients with headache is 'SNOOP-4', which is outlined below.[3]

- Systemic symptoms and signs, such as fever, myalgias and weight loss, could point to giant cell arteritis or an infection; systemic disease, such as malignancy and AIDS, suggests metastatic disease or an opportunistic CNS infection.
- Neurological symptoms or signs raise suspicion for structural, neoplastic, inflammatory or infectious CNS disease.
- Onset, as in sudden-onset conditions (e.g. thunderclap headache), could indicate an underlying stroke, subarachnoid haemorrhage, cerebral venous sinus thrombosis, RCVS or arterial dissection.
- Onset after 50 years of age suggests structural, neoplastic, inflammatory or infectious CNS disease, or giant cell arteritis.
- Pattern change (if there is a previous history) could point to progressive headache with loss of headache-free periods.
- Precipitated by Valsalva manoeuvre, which suggests Chiari malformations, structural lesions that obstruct cerebrospinal fluid flow or a cerebrospinal fluid leak.
- Postural aggravation, which is headache worsened by either standing or lying down, suggests intracranial hypotension from a cerebrospinal fluid leak or intracranial hypertension, respectively. Aggravation by certain neck movements and positioning might indicate cervicogenic headache.
- Papilloedema, when present, raises the suspicion of intracranial hypertension.

Investigations to reassure the patient

Most patients with recurrent or chronic headaches have primary headaches, therefore, investigations are likely to be normal. The patient often finds it difficult to believe that severe headache is not associated with structural brain pathology and sometimes imaging is needed to quell such fears. This often leaves the doctor feeling uncomfortable, either for ordering what seems to be an unnecessary test or for failing to allay the patient's concerns. In these cases, it is inadvisable to arrange an inadequate investigation that fails to definitively exclude the disorders causing concern.

If any imaging is contemplated, it is better to initially perform an MRI scan, rather than a CT scan, as CT findings often necessitate the patient subsequently undertake an MRI. MRI is clearly superior in excluding structural lesions that are likely to cause headache, and the radiation dose, which is an issue with CT, is not an issue with MRI. The practical difficulty is the policy of differential Medicare reimbursement for CT versus MRI when requested by a GP.

Patients with migraine or tension type headache are not immune to other disorders. A secure knowledge of the usual features of these disorders allows for recognition of a significant change that might imply alternative pathology.

Conclusion

Although there is no simple or global rule to guide the investigation of a patient with headache, a careful and focused clinical assessment, with particular emphasis on the tempo of the headache's evolution, can help establish a cause. The approach to investigation for recently developed headaches is greatly different from that of longstanding chronic or recurrent headaches. MT

References

1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders. 3rd ed. Cephalagia 2018; 38(Suppl 1): 1-211.
2. Lipton RB, Dodick D, Sadovsky R, et al. A self-administered screener for migraine in primary care: The ID Migraine(TM) validation study. Neurology 2003; 61: 375-382.
3. Silberstein SD, Lipton RB. In: Silberstein SD, Lipton RB, Dodick DW, eds. Wolff's headache and other head pain. 8th ed. New York: Oxford University Press; 2008: 315-377.

COMPETING INTERESTS: Professor Stark has served on advisory boards for Teva, Eli Lilly, AbbVie, Viatris and Lundbeck; and received payment for educational presentations from AbbVie, Teva, Eli Lilly and Viatris.

Migraine in 2025

An update on management

TAMSIN HILLIARD MB BS; **JASON C. RAY** MB BS, FRACP, PhD
ELSPETH J. HUTTON BMedSci(Hons), MB BS, FRACP, PhD
RICHARD J. STARK AM, MB BS, FRACP, FANZAN, MACLM

Migraine is a common and disabling neurological condition that affects quality of life. The three key treatment strategies for migraine are a personalised management approach addressing lifestyle factors, acute medications and preventive medications. With modern treatments, most patients can expect substantial improvement in symptoms and quality of life.

KEY POINTS

- Migraine has a significant impact on quality of life and is the second leading cause of disability worldwide.
- The four clinical phases of a migraine attack include prodrome, migraine aura, headache and postdrome.
- The ID-Migraine questionnaire can be used to identify patients with migraine in primary care, and screening for red flags for secondary headaches should be carried out using the SNNOOP10 list.
- Migraine can be managed using lifestyle management (reviewing sleep, exercise, diet and stress and keeping a headache diary), acute treatment and preventive treatment.
- Acute treatments include simple analgesics, NSAIDs, triptans and antiemetics. Newly available gepants (oral calcitonin gene-related peptide [CGRP] antagonists) have a role when triptans are not tolerated or are contraindicated.
- Preventive treatments involve selected oral medications and supplements, and advanced treatment options include onabotulinumtoxinA and CGRP monoclonal antibodies.

According to the Global Burden of Disease studies, migraine represents the second leading cause of disability worldwide and the leading cause of reversible disability in people under the age of 50 years.[1,2] In Australia, migraine affects about one in five people and is among the 20 most common conditions managed by GPs, being responsible for one in 100 GP encounters.[3] Unsurprisingly therefore, it is estimated to cost the economy AU$35.7 billion in direct health and indirect costs.[4]

Each year 2.5% of patients with migraine progress from episodic (less than 15 headache days per month) to chronic migraine (15 or more headache days per month), with associated negative impacts on quality of life and health resources.[5] The key modifiable risk factors contributing to the progression of disability are obesity, snoring, stressful events, depression or anxiety and significantly ineffective preventive treatment. These risk factors increase severity or frequency of migraine, leading to increased attack frequency and acute analgesic overuse.[5] This article updates our previous 2022 article[6] and outlines the diagnosis and management of migraine, highlighting the importance of careful assessment for differential diagnoses and an approach to management that includes lifestyle interventions and pharmacological treatment.

MedicineToday 2025; 26(7 Suppl): 8-15
First published in Medicine Today 2025; 26(6): 40-48

Dr Hilliard is a Neurologist at the Royal Hobart Hospital, Hobart, Tas. Dr Ray is a Neurologist in the Department of Neurology, Alfred Health and the Department of Neurology, Austin Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne. Dr Hutton is a Neurologist in the Department of Neurology, Alfred Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne. Professor Stark is a Neurologist in the Neurology Department, The Alfred Hospital, Melbourne; and Adjunct Clinical Professor in the Department of Neuroscience, Monash University, Melbourne, Vic.

Pathophysiology

The 20th century vascular theory of migraine is now recognised to be incomplete, and while the pathophysiology of migraine is complex and reviewed elsewhere, several key points bear

highlighting.[7,8] Although the trigger is still debated, imaging studies show that several brain regions, including the hypothalamus, are activated 24 to 72 hours before a migraine attack.[9] These studies provide a pathophysiological correlation for the four clinical phases of a migraine attack, which are prodrome, migraine aura, headache and postdrome (Figure 1).[7,10]

A migraine aura is believed to be caused by a spreading 'wave' of depolarisation and subsequent refractory period across a cortical region.[11] The pain of a migraine attack itself is caused by activation of the trigeminocervical complex in the brainstem, along with other pain circuits, and subsequent release of a variety of neuropeptides including calcitonin gene-related peptide (CGRP).[7,8] CGRP, which has emerged as a therapeutic target, acts on the trigeminovascular system, a complex system rich in CGRP and 5HT receptors that, as a potent vasodilator, causes the vascular changes originally observed in migraine.[12]

Presentation and assessment

Migraine is defined by the *International Classification of Headache Disorders*, third edition (ICHD-3) and further classified by frequency as either episodic or chronic and by the presence or absence of aura (Table 1).[13] The four phases of a migraine are described above. The headache phase is easily identified by the presence of pain; however, careful questioning can often identify features of a prodromal phase, such as yawning and increased urine production. Some prodromal symptoms such as neck stiffness and food cravings can be difficult to interpret because they might be regarded by the patient as migraine triggers.

Migraine aura is reported in 30% of patients and does not necessarily precede each headache. More than 95% of patients with aura experience a visual phenomenon, often a scintillating scotoma that may start centrally, often with jagged edges (fortification spectra) (Figures 2a and b).[14,15] Other manifestations may be sensory, motor, speech or, rarely, brainstem symptoms.

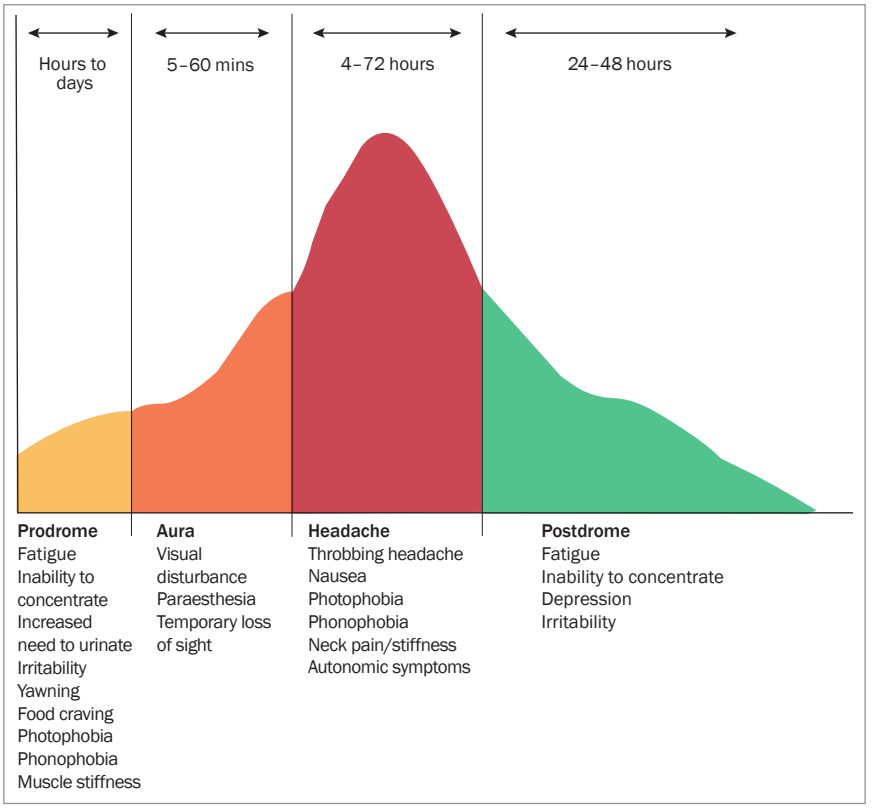


Figure 1. The four phases of a migraine attack.

Aura causes fully reversible, typically unilateral symptoms. Certain features help to distinguish it from important differential diagnoses. Migraine aura develops gradually, evolving over 10 to 30 minutes, lasting 5 to 60 minutes and often consisting of positive symptoms (paraesthesia) followed by negative symptoms (numbness). Transient ischaemic attack, by contrast, begins suddenly, persists for minutes to hours, generally as negative symptoms, and only affects cranial vascular territories. Focal seizures also progress gradually (such as with a Jacksonian march), but are of shorter duration, lasting less than two minutes.[16]

The pain phase of a migraine attack is often unilateral at onset; however, there is often bilateral pain, so unlike some other conditions such as cluster headache, migraine is generally not side-locked.[17] Pain may be throbbing in character and typically lasts from four to 72 hours.[13] Features that differentiate migraine pain from other headaches include worsening with physical activity and the migrainous phenomena of nausea, or photophobia and phonophobia, so the symptoms cause many patients to avoid activity and lie down in a dark room.[13] Finally, a postdrome may be identified and include symptoms of fatigue, depression, irritability and reduced concentration (Figure 1).

Diagnosis

Migraine is a clinical diagnosis and further investigation should only be considered in the appropriate clinical context.[18] The ID-Migraine questionnaire is a useful screening tool to help identify patients with migraine in primary care (Box 1)[18] and should be performed alongside screening for red flags for secondary headaches using the SNNOOP10 red flags for secondary headaches criteria (Table 2).[19,20]

Hypothyroidism and vitamin D and iron deficiency may be associated with increased

TABLE 1. ***INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS*** **(ICHD-3) CLASSIFICATION OF MIGRAINE[13]**

Type	Criteria
Episodic	Headache present for less than 15 days a month
Chronic	Headache present for 15 days or more in a month, with 8 or more days meeting the criteria for migraine
Migraine without aura	At least five attacks fulfilling the following criteria: • headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated) • headache has at least two of the following four characteristics: – unilateral location – pulsating quality – moderate or severe pain intensity – aggravation by or causing avoidance of routine physical activity • during headache at least one of the following: – nausea and/or vomiting – photophobia and phonophobia • not better accounted for by another ICHD-3 diagnosis
Migraine with aura	At least two attacks fulfilling the following criteria: • one or more of the following fully reversible aura symptoms: – visual – sensory – speech and/or language – motor – brainstem – retinal • at least three of the following six characteristics: – at least one aura symptom spreads gradually over 5 minutes – two or more aura symptoms occur in succession – each individual aura symptom lasts five to 60 minutes – at least one aura symptom is unilateral – at least one aura symptom is positive – the aura is accompanied, or followed within 60 minutes, by headache • not better accounted for by another ICHD-3 diagnosis

headache frequency and should be identified and treated.[21-23] Because incidental findings, found in 2% of the general population, may increase distress and provoke further unproductive investigation, routine neuroimaging is not recommended for patients with a normal neurological examination and no atypical headache features or red flags.[24,25] Specific consideration should be given to important mimics that may be differentiated on history and include the following.[26]

- Cluster headache – presents with excruciating, strictly side-locked pain over the temple and orbital region, with accompanying agitation and cranial autonomic features (e.g. tearing, nasal congestion).[27] Differentiated from migraine by its side-locked pain and agitation, cluster headaches are typically shorter (averaging 90 minutes) and typically exhibit circadian (classically one to two hours after sleep onset) and circannual periodicity (bouts occur at the same time of year, typically in autumn and spring).
- Hemicrania continua – presents with strictly side-locked pain that is continuous from onset.[13] Differentiated from migraine by its side-locked and continuous nature,

Figure 2. Visual phenomena often experienced during migraine with aura. Example of a central scotoma (a, left) and scintillating scotoma or fortification spectra (b, right). Visual phenomenon effects made in ©BioRender (biorender.com).

1. ID-MIGRAINE CRITERIA[18]

During the past three months, have you ever experienced any of the following symptoms concerning your headache pain?

- Have you felt nauseated or sick to your stomach during headache pain?
- Has light bothered you during a headache (or more than when you do not have headaches)?
- Have your headaches limited your ability to work, study or do what you needed to do for at least one day?

TABLE 2. SNNOOP10 LIST OF RED FLAGS FOR SECONDARY HEADACHE DISORDERS[20]

Red flag	Possible secondary headache disorder
Systemic symptoms	Intracranial infection
Neoplasm	Metastatic disease
Neurological deficit	Stroke, abscess or infection
Onset of headache is abrupt	Subarachnoid haemorrhage, venous sinus thrombosis, reversible cerebral vasoconstriction syndrome, haemorrhage
Older age (above 50 years)	Giant cell arteritis, neoplasm, stroke
Pattern change, progressive or new onset	Neoplasms, vascular abnormality
Positional headache	Intracranial hypertension or hypotension
Preceded by sneezing, coughing or exercise	Posterior fossa malformations, Chiari malformation
Papilloedema	Intracranial hypertension, mass lesion, venous sinus thrombosis
Pregnancy or puerperium	Postdural headache, pre-eclampsia, venous sinus thrombosis, pituitary apoplexy, hypothyroidism
Painful eye with autonomic features	Pathology in posterior fossa, pituitary region or cavernous sinus, Tolosa-Hunt syndrome, ophthalmic causes
Abnormality of the immune system	Opportunistic infection or metastasis
Painkiller overuse or new drug	Medication overuse headache, drug incompatibility

it may also present with agitation and autonomic symptoms.

- New daily persistent headache – differentiated from migraine by its unremitting (persistent) nature and clearly remembered day of onset.
- Tension-type headache – described as a featureless headache, it is distinguished from migraine by shorter and less disabling attacks with an absence of migrainous features (i.e. throbbing pain, nausea, photophobia or phonophobia).[13]
- Sinus headache – although often diagnosed from imaging findings or frontal tenderness, headache caused by chronic sinusitis is relatively rare. In one formative study, 81% of patients with the label actually had migraine and management was delayed by an average of 7.8 years.[28]

Approach to management

The management of migraine can be broken into three pillars: lifestyle management, acute treatment and preventive treatment. All patients benefit from lifestyle management and optimisation of acute treatment, whereas patients with four or more migraine days a month or attacks that are difficult to control may benefit from preventive treatment.

Lifestyle management

Lifestyle management is likely an effective treatment that affords patients autonomy over their health. Studies on lifestyle interventions in managing migraine are limited; however, some suggest engaging in regular positive lifestyle behaviours may help limit episodes of chronic migraine, with a number needed to treat of just two in a population of people with chronic migraine.[29] The mnemonic SEEDS (sleep, exercise, eating, diary, stress) is a useful framework for framing a discussion around lifestyle management.[30]

Sleep

Although snoring is a risk factor for progression to chronic migraine, obstructive sleep apnoea does not occur more frequently in patients with migraine.[31,32] The presence of sleep-disordered breathing, early morning headaches or daytime somnolence should, however, prompt further investigation for obstructive sleep apnoea as a modifiable factor in people with migraine. A bidirectional relationship may exist between migraine and insomnia, with a further association with frequency and severity of migraine attacks.[33]

Strategies to improve sleep quality include sleep restriction, improved sleep hygiene and stimulus control. Cognitive behavioural therapy for insomnia has also been shown to improve headache frequency.[34] The Sleep Health Foundation has detailed resources that are of benefit (https://www.sleephealthfoundation.org.au).

Exercise

A recent meta-analysis of 265 studies found that aerobic exercise of 30 to 50 minutes, three to five times a week over six weeks has a modest effect on the frequency of migraine attacks.[35] Exercise was also shown to be noninferior to pharmacotherapy and patients saw an additive benefit of therapies.[30] A graded exercise program is important for improving tolerability in patients with migraine.

2. SELECTED ACUTE TREATMENT OPTIONS FOR MIGRAINE[45]

First-line treatment
- Aspirin 900 mg
- Ibuprofen 600 mg
- Naproxen 750 mg
- Paracetamol 1 g

Triptans
- Eletriptan 40 to 80 mg
- Naratriptan 2.5 mg
- Rizatriptan 10 mg
- Sumatriptan 50 mg
- Zolmitriptan 2.5 mg

For nausea
- Metoclopramide 10 mg
- Ondansetron 4 mg

In analgesic overuse
- Naproxen 750 mg for 2 weeks
- Prednisolone 50 mg for 3 days, then 25 mg for 3 days then 12.5 mg for 3 days

Alternative preparations*
- Diclofenac per rectum
- Prochlorperazine per rectum (compounded)
- Rizatriptan wafer (oral absorption)
- Sumatriptan injection (generic form)
- Sumatriptan nasal spray (not currently available in Australia)

* Non-oral absorption (except wafer), making these valuable in patients with nausea.

Eating (diet)

Dietary triggers of migraine are reported by up to one-third of patients, with 44%, 27% and 7.5% reporting migraines triggered by fasting, alcohol consumption and chocolate consumption, respectively.[36,37] However, the role of specific dietary triggers should be interpreted carefully as the hypothalamic activation and food craving that often precede an attack can be mistaken for triggers.[7,9,36] For example, one double-blinded study showed that chocolate did not trigger migraines.[38]

Dietary advice should be practical and focus on avoiding general triggers, such as fasting, and making dietary choices to maintain stable blood glucose levels.[39,40] Although the role of caffeine in migraine is not fully understood, abrupt withdrawal from caffeine can potentiate headaches, with a dose-dependent relationship between cessation and withdrawal symptoms.[41] A gradual reduction to the minimum tolerable level or a maximum of 200 mg of caffeine per day (two cups of coffee) is a reasonable approach.[42] Several dietary interventions show improvement in headache frequency, including low-fat, low glycaemic and Mediterranean diets, and may be recommended to patients.[3] Dietary triggers for migraine vary greatly between patients, so a generic list of foods to be avoided is not especially helpful.

Diary

Keeping a headache diary is recommended to help monitor disease activity, effectiveness of preventive treatment and frequency of analgesic use. Headache diary templates are available on the Australian and New Zealand Headache Society website (https://anzheadachesociety.org/for-patients). Electronic versions are available for smart devices.

Stress

The causal relationship between stress and migraine remains unclear; however, periods of stress are associated with both new-onset migraine and transformation to chronic migraine, and change in levels of stress (both increased and decreased) are a risk factor for a migraine attack.[43] Accordingly, stress-centred interventions for managing migraine, such as relaxation therapy, cognitive behavioural therapy and biofeedback, are supported by grade A evidence.[44]

Acute treatments

The goal of the acute treatment of migraine is pain freedom within two hours. This may be achieved through monotherapy with a simple analgesia or, if analgesia alone is ineffective, by the addition of a triptan or an antiemetic (Box 2).[45] Some key principles to enhance efficacy include:

- analgesics are more effective when taken early during an attack[46]
- a combination of analgesics is more effective than monotherapy[46]
- beyond the antiemetic effect, metoclopramide provides additional analgesic effect and improves the response to other analgesics.[47,48]

Nonpharmacological interventions, such as meditation and ice-packs, have also shown effect.[49,50]

Triptans

In patients without a significant vascular history, triptans are an effective treatment. Studies have shown they achieved pain freedom as monotherapy in 18 to 50% of cases.[51] Initial triptan selection is often based on the dosage form or route of administration – for patients with prominent early nausea, sumatriptan is available as a nonoral preparation, and rizatriptan wafers are dissolved on the tongue before swallowing for oral absorption. In patients who do not have initial pain relief with other triptans, switching to eletriptan 80 mg or rizatriptan 10 mg may be more effective.[52] In patients in whom analgesia has a waning effect, longer-acting analgesics such as naratriptan or naproxen may be preferable.

Gepants and ditans

Two new classes of drugs for acute treatment have become available in recent years: gepants and ditans. The gepants are oral CGRP antagonists. At present, only rimegepant is available in Australia, but other drugs may become available in the future. Currently, rimegepant is not PBS funded, making it more expensive than triptans. It may be valuable where the use of triptans is limited by side effects or concern about potential cardiovascular complications, or where the frequency of triptan use raises concerns about medication overuse headache (MOH).[53-55] Gepants are thought to carry a much lower risk of causing MOH than triptans.[55]

Ditans are 5HT1F receptor agonists that appear to have less potential for vascular side effects than triptans.[54] The first of this class (lasmiditan) is available overseas, but not yet in Australia.

A recent guideline from the International Headache Society provides practical advice on acute therapy in various situations.[56] It emphasises the value of triptans and notes that some treatment options are not universally available. The guidelines are summarised in Table 3.[56]

A systematic review and network meta-analysis of medication for acute migraine treatment confirmed the clinical impression that, in general, triptans are more effective than gepants or ditans.[57] The authors concluded that overall, eletriptan, rizatriptan, sumatriptan and zolmitriptan were more efficacious than rimegepant, lasmiditan and ubrogepant (the latter two are not yet available for use in Australia). The newer agents have a place when side effects or concerns about cardiovascular risk or medication overuse limit the use of triptans.

Overuse of acute medications

Overuse of acute analgesia for any reason predisposes patients with migraine to developing a secondary headache, MOH.[13] MOH occurs as a result of further sensitisation of the pain circuits of the brain and diminished ability to inhibit painful signals, resulting in headaches that are more frequent and refractory to both acute and preventive treatments.[58] Unfortunately, up to 70% of patients with chronic daily headaches suffer comorbid MOH.[59]

Prevention is the best treatment for MOH, and patients must be counselled to not exceed 10 days of triptan use per month, or 15 days total for simple analgesics.[13] Opiates are not recommended for migraine by the authors because of potential issues of both MOH and dependence. Few studies exist for MOH management; however, in conjunction with preventive treatments, bridging strategies, including use of slow-release naproxen (for triptan overuse) or prednisolone and withdrawal (although evidence for this is limited and mixed), are recommended (Box 2).[26,45,55,60]

Preventive treatments

Preventive treatment for migraine is indicated to limit the impact of migraine and risk of acute analgesic overuse for patients who have more than four days of migraine per month or those with disabling disease.[61]

Oral medications

Selected oral medications are outlined in Table 4.[62,63] Although evidence based,

TABLE 3. QUESTIONS ON THE USE OF ACUTE THERAPY FOR MIGRAINE, FROM THE INTERNATIONAL HEADACHE SOCIETY GUIDELINES[56]

Question	Brief answer*
Q1. Should triptans be used when analgesics and NSAIDs are ineffective?	• Yes
Q2. If a triptan is only partially effective, should the dose be increased?	• Yes
Q3. If people with migraine are not responding to the first triptan, should they switch to another triptan?	• Yes
Q4. In people with migraine with nausea and/or vomiting, should antiemetics be combined with analgesics, NSAIDs or triptans?	• Yes
Q5. If triptans are only partially effective, should a combination of NSAIDs and triptans be used?	• Yes
Q6. Do gepants and lasmiditan† have a role in treating migraine attacks?	• Yes, if triptans are ineffective or not tolerated
Q7. Are ergot derivatives an option for treating migraine attacks?	• Can be considered if safer alternatives have failed
Q8. What is the recommended timing of administration of acute treatment?	• As early as possible
Q9. Which treatment options are available for individuals who experience early vomiting during a migraine attack?	• Consider nonoral preparations
Q10. How can headache relapse be treated following the initial successful treatment of a migraine attack?	• Second dose of same medication then switch to a different one
Q11. How should migraine attacks that persist for more than 72 hours (status migrainosus) be treated?	• Various options including intramuscular NSAID or subcutaneous sumatriptan
Q12. What is the maximum number of days that acute medications can be administered without increased risk of developing medication overuse headache?	• NSAIDs <10 days per month • Triptans <8 days per month
Q13. Which treatment options are preferable during pregnancy and breastfeeding?	• Paracetamol • Triptans with caution
Q14. What drugs can be used in children and adolescents with a migraine attack?	• Paracetamol or ibuprofen • Triptans as second-line treatment
Q15. What drugs are preferred in people over 65 years of age with a migraine attack?	• Depends on comorbidities
Q16. What is the recommended approach to the acute treatment of migraine in people with a history of stroke, other vascular diseases or uncontrolled hypertension?	• Paracetamol as first-line treatment • Ditan or gepant as second-line treatment
Q17. What are possible treatment approaches to menstrual migraine?	• Usual options • Mini-prophylaxis as second-line treatment

*These answers are oversimplications; the guidelines provide a detailed, more nuanced and evidence-based rationale, as well as 'optimal' and 'essential' recommendations.
†Lasmiditan is not currently TGA approved.

TABLE 4. SELECTED PREVENTIVE ORAL TREATMENTS FOR MIGRAINE[62,63]

Medication	Typical therapeutic dose range	PBS status	Potential benefits	Caution
Propranolol	40 to 120 mg twice daily	GB-M	Use in tremor, anxiety	Asthma
Candesartan	8 to 32 mg daily	GB-O	Low side-effect profile, use in hypertension	Use with NSAIDs and diuretics, hyperkalaemia, hypotension
Topiramate	25 to 100 mg twice daily	Auth-M	Weight loss	Depression, renal calculi, glaucoma
Sodium valproate	200 to 600 mg twice daily	GB-O	Mood stabilising	Teratogenicity, weight gain
Amitriptyline	10 to 75 mg at night	GB-O	Use in insomnia, bruxism, depression and anxiety	Sedation, weight gain
Venlafaxine	75 to 150 mg daily	RB-O	Use in insomnia, depression or anxiety	Use with other tricyclic antidepressants or selective serotonin reuptake inhibitors
Verapamil	80 to 240 mg daily	GB-O	Lowers blood pressure, benefit in cluster headache	Hypotension, constipation, cardiac conduction problems
Pizotifen	0.5 to 2 mg daily	GB-M	Sedation	Sedation, weight gain

Abbreviations: Auth-M = streamlined authority for migraine; GB-M = general benefit for migraine; GB-O = general benefit for other condition; RB-O = restricted benefit for other condition.

several preventive treatments for migraine are available for off-label use on the PBS. Guiding principles for the use of oral preventive treatments for migraine include:

- given no preventive oral medication is clearly superior, the choice of medication is best guided by side effect profile, comorbidity and patient preference
- in the absence of side effects, medications should be continued for a minimum of eight to 12 weeks at a moderate dose to assess efficacy
- in the absence of side effects, the dose should be titrated to assess efficacy and optimise response.

Supplements

Some patients may prefer supplements for migraine prevention; however, evidence for their efficacy is limited and mixed. Some studies suggest magnesium, riboflavin, coenzyme Q10 and cholecalciferol are effective and safe for migraine prevention.[22,64] Vitamin D deficiency has been shown and mitochondrial energy depletion suggested in people with migraines.[22,65] Evidence suggests the following supplemental treatment may be considered for suitable patients:

- 400 to 600 mg of magnesium (elemental) daily[66]
- 200 mg of riboflavin daily[60]
- 150 to 300 mg of coenzyme Q10 daily[60]
- replacement of vitamin D to normal levels.[67]

OnabotulinumtoxinA and CGRP monoclonal antibodies

Advanced treatment options are available for patients with chronic migraine in whom three preventive medications have not been effective or are contraindicated and any comorbid MOH has been addressed. These advanced treatments include onabotulinumtoxinA (OnaB-A) and the CGRP monoclonal antibodies (mAbs) fremanezumab and galcanezumab (given as monthly subcutaneous injections to the stomach or thighs) and eptinizumab (given by intravenous infusion every three months).

OnaB-A must be started by a neurologist, and CGRP mAbs may be prescribed by GPs as either initiating or continuing treatment in shared care with a neurologist. OnaB-A is given as a series of 31 subcutaneous injections through the head and neck at 12-weekly intervals and may be particularly useful for patients with neck-muscle activation, bruxism or multiple comorbidities because of its limited systemic uptake.

The PBS requirements to prescribe these injectables include formal headache diaries that record headache and migraine frequency. Unnecessary delays in treatment can be avoided if these are available when the patient sees a neurologist. The updated PBS criteria may result in the GP specialist leading the assessment of response to initial therapy. In this case, there is some important nuance in the PBS criteria.

To continue treatment, the PBS criteria for OnaB-A require patients to achieve at least a 50% reduction in headache days per month (i.e. any form of headache) compared with baseline (assessed at six months), whereas CGRP mAbs require at least a 50% reduction in migraine days compared with baseline (assessed at three months). These migraine days are often identifiable by the presence of photophobia, nausea or activity restriction. Specific evaluation for these outcomes is not only clinically valuable in helping decide whether to persist with or change treatment but is administratively vital to document the PBS criteria that allow a therapy to be continued. PBS criteria are summarised in Table 5.[68]

Although there are no high-quality data assessing the relative efficacy of OnaB-A and CGRP mAbs, both have

TABLE 5. PBS CRITERIA FOR ONABOTULINUMTOXINA AND THE CGRP MONOCLONAL ANTIBODIES[68]

	OnabotulinumtoxinA	Galcanezumab	Fremanezumab	Eptinezumab
Number of MHD and MMD required for initial treatment	≥15 MHD and ≥8 MMD	≥15 MHD and ≥8 MMD	≥8 MMD	≥15 MHD and ≥8 MMD
Reduction by ≥50% in MHD or MMD required to continue treatment	MHD over six months	MMD over three months	MMD over three months	MMD over three months
Who can prescribe?	Must be treated by a neurologist	Must be treated in consultation with a neurologist	Must be treated in consultation with a neurologist	Must be treated in consultation with a neurologist
Restrictions common to all four treatments	• Patient must have experienced: an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications before commencement of treatment with this drug for this condition – prophylactic migraine medications are: propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate • Patient must be appropriately managed by their practitioner for medication overuse headache before initiation of treatment with this drug • Patient must be at least 18 years of age			

Abbreviations: CGRP = calcitonin gene-related peptide; MHD = monthly headache days; MMD = monthly migraine days.

shown efficacy in treating headaches in clinical trials. OnaB-A achieved a 50% or greater improvement in headaches in 47.1% of patients.[69] CGRP mAbs showed a 50% or greater reduction in headaches in 30 to 40% of patients.[70]

The oral CGRP antagonist rimegepant can also be used for prophylaxis in episodic migraine (migraine days on <15 days per month), given at a dose of 75 mg every second day.[71] As rimegepant is not yet PBS funded, it is more expensive than other options. It can have a practical use, however, to provide short-term cover at times of high risk for migraine breakthrough. For example, patients who have migraines reappearing towards the end of the 12 weeks between OnaB-A injections may find this strategy helpful. Some patients may use a short course for menstrual migraine mini-prophylaxis or to protect against migraines at crucial times such as weddings or exams.

Common, theoretical and potential side effects of CGRP antagonists

Overall, gepants and CGRP mAbs have been well tolerated, with a few shared side effects. Local injection site reactions occur in about 5% of patients who use CGRP mAbs. The most common side effect appears to be constipation (although perhaps more commonly with the CGRP mAb erenumab, which is currently not available in Australia). Real-world data suggest constipation may occur in 10 to 20% of patients who use CGRP mAbs, as opposed to the 1.4 to 2.1% reported in trials.[72]

As CGRP is widely expressed throughout the body, theoretically off-target effects of blockade may be possible. There is little evidence yet of problems from coronary or cerebral vasoconstriction, but slight worsening of hypertension has been noted.[73,74] There have been anecdotal reports of occasional aggravation of inflammatory disorders such as psoriasis from CGRP mAbs.[75]

As for most new medications, there is no experience in the paediatric or geriatric population and no human data on use during pregnancy or lactation. CGRP has a role in placental development, so use by pregnant or breastfeeding women is not recommended. Because of the long half-life of CGRP mAbs, they should be ceased at least five months before pregnancy.[76]

Conclusion

Migraine is a common presentation in clinical practice that requires a comprehensive approach to management. Important differential diagnoses should be assessed in the context of the four clinical phases of migraine. Addressing lifestyle factors that may contribute to migraine can help reduce migraine frequency and morbidity. Pharmacological treatments include acute and preventive medications and should be used appropriately to optimise response and reduce acute analgesic overuse. MT

References

A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2025/july/supplements/focus-headache-collection).

COMPETING INTERESTS: Dr Hilliard: None.
Dr Ray has received honoraria for educational presentations for AbbVie, Novartis and Viatris; has served on medical advisory boards for Pfizer, Viatris and Eli Lilly; and his institution has received funding for research grants, clinical trials and projects supported by the International Headache Society, Brain Foundation, Lundbeck, AbbVie, Pfizer and Aeon.
Dr Hutton has served on advisory boards for Sanofi-Genzyme, Novartis, Teva, Eli Lilly, Allergan and Lundbeck; been involved in clinical trials sponsored by Novartis, Teva, Xalud and Cerecin; and received payment for educational presentations from Allergan, Teva, Eli Lilly and Novartis.
Professor Stark has served on advisory boards for Teva, Eli Lilly, AbbVie, Viatris and Lundbeck; and received payment for educational presentations from AbbVie, Teva, Eli Lilly and Viatris.

MedicineToday 2025; 26(1 Suppl): 8-15
First published in Medicine Today 2025; 26(6): 40-48

Migraine in 2025
An update on management

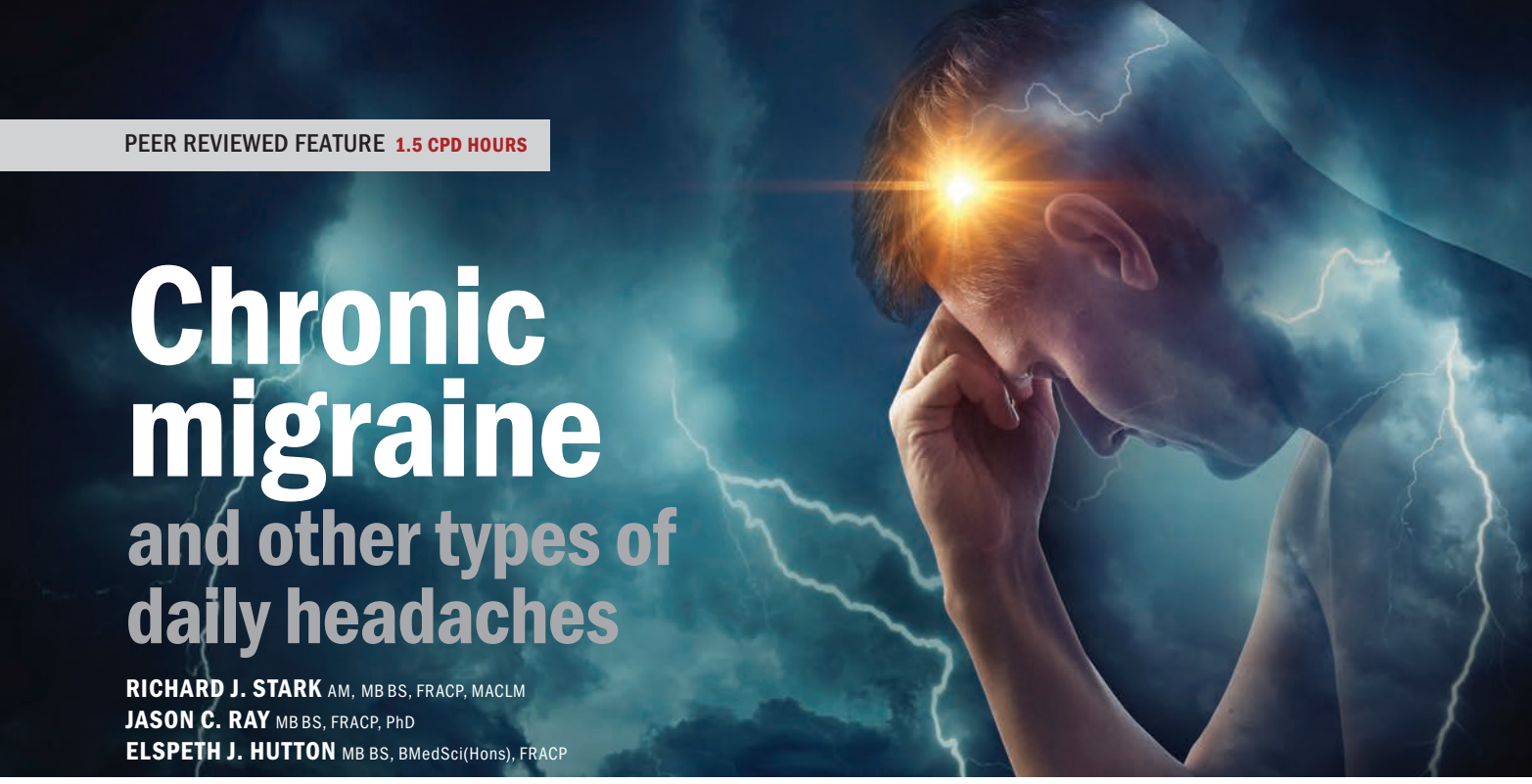
TAMSIN HILLIARD MB BS; **JASON C. RAY** MB BS, FRACP, PhD
ELSPETH J. HUTTON BMedSci(Hons), MB BS, FRACP, PhD
RICHARD J. STARK MB BS, FRACP, FANZAN, MACLM

References

1. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1789-858.
2. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain 2018; 19: 17-20.
3. Britt H, Miller GC, Henderson J, et al. General practice activity in Australia 2015–16. General practice series no. 40. Sydney: Sydney University Press; 2015. Available online at: https://ses.library.usyd.edu.au/handle/2123/15514 (accessed July 2025).
4. Deloitte Access Economics. Migraine in Australia whitepaper. Measuring the impact. Canberra: Deloitte; 2018. Available online at: https://www.deloitte.com/au/en/services/economics/perspectives/migraine-australia-whitepaper.html (accessed May 2025).
5. Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. Curr Pain Headache Rep 2011; 15: 70-78.
6. Hilliard T, Ray JC, Hutton EJ, Stark RJ. Migraine in 2022: an update on management. Medicine Today 2022; 23: 57-64.
7. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev 2017; 97: 553-622.
8. Ashina M. Migraine. New Engl J Med 2020; 383: 1866-1876.
9. Karsan N, Goadsby PJ. Imaging the premonitory phase of migraine. Front Neurol 2020; 11: 140.
10. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 1992; 12: 221-228.
11. Charles AC, Baca SM. Cortical spreading depression and migraine. Nat Rev Neurol 2013; 9: 637-644.
12. Marichal-Cancino BA, González-Hernández A, Guerrero-Alba R, Medina-Santillán R, Villalón CM. A critical review of the neurovascular nature of migraine and the main mechanisms of action of prophylactic antimigraine medications. Expert Rev Neurother 2021; 21: 1035-1050.
13. International Headache Society. The International Classification of Headache Disorders 3rd edition. London: International Headache Society; 2021. Available online at: https://ichd-3.org/ (accessed July 2025).
14. Viana M, Tronvik EA, Do TP, Zecca C, Hougaard A. Clinical features of visual migraine aura: a systematic review. J Headache Pain 2019; 20: 64.
15. Kim KM, Kim BK, Lee W, Hwang H, Heo K, Chu MK. Prevalence and impact of visual aura in migraine and probable migraine: a population study. Sci Rep 2022; 12: 426.
16. Jenssen S, Gracely EJ, Sperling MR. How long do most seizures last? A systematic comparison of seizures recorded in the epilepsy monitoring unit. Epilepsia 2006; 47: 1499-1503.
17. Leone M, Frediani F, Torri W, et al. Clinical considerations on side-locked unilaterality in long-lasting primary headaches. Headache 1993; 33: 381-384.
18. Ray JC, Hutton EJ. Diagnostic tests: imaging in headache disorders. Aust Prescrib 2022; 45: 88-92.
19. Cousins G, Hijazze S, Van de Laar FA, Fahey T. Diagnostic accuracy of the ID migraine: a systematic review and meta-analysis. Headache 2011; 51: 1140-1148.
20. Do TP, Remmers A, Schytz HW, et al. Red and orange flags for secondary headaches in clinical practice. Neurology 2019; 92: 134-144.
21. Spanou I, Bougea A, Liakakis G, et al. Relationship of migraine and tension-type headache with hypothyroidism: a literature review. Headache 2019; 59: 1174-1186.
22. Ghorbani Z, Togha M, Rafiee P, et al. Vitamin D in migraine headache: a comprehensive review on literature. Neurol Sci 2019; 40: 2459-2477.
23. Tayyebi A, Poursadeghfard M, Nazeri M, Pousadeghfard T. Is there any correlation between migraine attacks and iron deficiency anemia? A case-control study. Int J Hematol Oncol Stem Cell Res 2019; 13: 164-171.
24. Evans RW, Burch RC, Frishberg BM, et al. Neuroimaging for migraine: the American Headache Society systematic review and evidence-based guideline. Headache 2020; 60: 318-336.
25. Morris Z, Whiteley WN, Longstreth WT, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2009; 339: b3016-b3016.
26. Ray JC, Macindoe C, Ginevra M, Hutton EJ. The state of migraine: an update on current and emerging treatments. Aust J Gen Pract 2021; 50: 915-921.
27. Ray JC, Stark RJ, Hutton EJ. Cluster headache in adults. Aust Prescr 2022; 45: 15-20.
28. Al-Hashel JY, Ahmed SF, Alroughani R, Goadsby PJ. Migraine misdiagnosis as a sinusitis, a delay that can last for many years. J Headache Pain 2013; 14: 97.
29. Agbetou M, Adoukonou T. Lifestyle modifications for migraine management. Front Neurol 2022; 13: 719467.
30. Robblee J, Starling AJ. SEEDS for success: lifestyle management in migraine. Cleve Clin J Med 2019; 86: 741-749.
31. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol; 2016; 12: 455-464.
32. Kristiansen HA, Kværner KJ, Akre H, Øverland B, Russell MB. Migraine and sleep apnea in the general population. J Headache Pain 2011; 12: 55-61.
33. Tiseo C, Vacca A, Felbush A, et al. Migraine and sleep disorders: a systematic review. J Headache Pain 2020; 21: 126.
34. Smitherman TA, Kuka AJ, Calhoun AH, et al. Cognitive-behavioral therapy for insomnia to reduce chronic migraine: a sequential bayesian analysis. Headache 2018; 58: 1052-1059.
35. Lemmens J, De Pauw J, Van Soom T, et al. The effect of aerobic exercise on the number of migraine days, duration and pain intensity in migraine: a systematic literature review and meta-analysis. J Headache Pain 2019; 20: 16.
36. Hindiyeh NA, Zhang N, Farrar M, Banerjee P, Lombard L, Aurora SK. The role of diet and nutrition in migraine triggers and treatment: a systematic literature review. Headache 2020; 60: 1300-1316.
37. Tai MLS, Yap JF, Goh CB. Dietary trigger factors of migraine and tension-type

headache in a South East Asian country. J Pain Res 2018; 11: 1255-1261.
38. Marcus D, Scharff L, Turk D, Gourley L. A double-blind provocative study of chocolate as a trigger of headache. Cephalalgia 1997; 17: 855-862.
39. Abu-Salameh I, Plakht Y, Ifergane G. Migraine exacerbation during Ramadan fasting. J Headache Pain 2010; 11: 513-517.
40. Nas A, Mirza N, Kahlho J, et al. Impact of breakfast skipping compared with dinner skipping on regulation of energy balance and metabolic risk. Am J Clin Nutr 2017; 105: 1351-1361.
41. Nowaczewska M, Wicí Nski M, Ka´zmierczak W. The ambiguous role of caffeine in migraine headache: from trigger to treatment. Nutrients 2020; 33: 381-384.
42. Silverman K, Evans SM, Strain EC, Griffiths RR. Withdrawal syndrome after the double-blind cessation of caffeine consumption. N Engl J Med 1992; 327: 1109-1114.
43. Stubberud A, Buse DC, Kristoffersen ES, Linde M, Tronvik E. Is there a causal relationship between stress and migraine? Current evidence and implications for management. J Headache Pain 2021; 22: 155.
44. The American Headache Society position statement on integrating new migraine treatments into clinical practice. Headache 2019; 51: 1-18.
45. Mounds R, Aplin P, Boundy K, et al. Acute treatment for migraine with a triptan. In: Therapeutic Guidelines. Melbourne: Therapeutic Guidelines Limited; 2017.
46. Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. Cochrane Database Syst Rev 2016; 4(4): CD008541.
47. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. Headache 2003; 43: 729-733.
48. Friedman BW, Irizarry E, Williams A, et al. A randomized, double-dummy, emergency department-based study of greater occipital nerve block with bupivacaine vs intravenous metoclopramide for treatment of migraine. Headache 2020; 60: 2380-2388.
49. Fichtel A, Larsson B. Does relaxation treatment have differential effects on migraine and tension-type headache in adolescents? Headache 2001; 41: 290-296.
50. Ucler S, Coskun O, Inan LE, Kanatli Y. Cold therapy in migraine patients: open-label, non-controlled, pilot study. Evid Based Complement Alternat Med 2006; 3: 489-493.
51. Cameron C, Kelly S, Hsieh SC, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. Headache 2015; 55: 221-235.
52. Xu H, Han W, Wang J, Li M. Network meta-analysis of migraine disorder treatment by NSAIDs and triptans. J Headache Pain 2016; 17: 113.
53. Lipton RB, Blumenfeld A, Jensen CM, et al. Efficacy of rimegepant for the acute treatment of migraine based on triptan treatment experience: pooled results from three phase 3 randomized clinical trials. Cephalalgia 2023; 43.
54. Mathew S, Ailani J. Traditional and novel migraine therapy in the aging population. Curr Pain Headache Rep 2019; 23: 42.
55. Croop R, Berman G, Kudrow D, et al. A multicenter, open-label long-term safety study of rimegepant for the acute treatment of migraine. Cephalalgia 2024; 44.
56. Puledda F, Sacco S, Diener H-C, et al. International Headache Society global practice recommendations for the acute pharmacological treatment of migraine. Cephalalgia 2024; 44.
57. Karlsson WK, Ostinelli EG, Zhuang ZA, et al. Comparative effects of drug interventions for the acute management of migraine episodes in adults: systematic review and network meta-analysis. BMJ 2024; 386: e080107.
58. Meng ID, Dodick D, Ossipov MH, Porreca F. Pathophysiology of medication overuse headache: insights and hypotheses from preclinical studies. Cephalalgia 2011; 31: 851-860.
59. Westergaard ML, Hansen EH, Glümer C, Olesen J, Jensen RH. Definitons of medication overuse headache in population-based studies and their implications on prevalence estimates: a systematic review. Cephalalgia 2014; 34(6): 409-425.
60. Diener H, Dodick D, Evers S, et al. Pathophysiology, prevention, and treatment of medication overuse headache. Lancet Neurol 2019; 18: 891-902.
61. Ailani J, Burch RC, Robbins MS. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. Headache 2021; 61: 1021-1039.
62. Evers S, Áfra J, Frese A, et al. EFNS guideline on the drug treatment of migraine - revised report of an EFNS task force. Eur J Neurol 2009; 16: 968-981.
63. Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. Headache 2012; 52: 930-945.
64. Tepper S. Nutraceutical and other modalities for the treatment of headache. Continuum 2015; 21: 1018-1031.
65. Welch K Ramadan, N. Mitochondria, magnesium and migraine. J Neurol Sci 1995; 134: 9-14.
66. Rajapakse T, Pringsheim T. Nutraceuticals in migraine: a summary of existing guidelines for use. Headache 2016; 56: 808-816.
67. Rapisarda L, Mazza MR, Tosto F, Gambardella A, Bono F, Sarica A. Relationship between severity of migraine and vitamin D deficiency: a case-control study. Neurol Sci 2018; 39(Suppl 1): 167-168.
68. Australian Government. Pharmaceutical Benefits Scheme. Canberra: Australian Government; 2025. Available online at: https://www.pbs.gov.au/pbs/home (accessed May 2025).
69. Ray JC, Hutton EJ, Matharu M. OnabotulinumtoxinA in migraine: a review of the literature and factors associated with efficacy. J Clin Med 2021; 10: 2898.
70. Ray JC, Kapoor M, Stark RJ, et al. Calcitonin gene related peptide in migraine: current therapeutics, future implications and potential off-target effects. J Neurol Neurosurg Psychiatry 2021; 92: 1325-1334.
71. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet 2021; 397: 51-60.
72. Ray JC, Kapoor M, Stark RJ, et al. Calcitonin gene related peptide in migraine: current therapeutics, future implications and potential off-target effects. J Neurol Neurosurg Psychiatry 2021; 92: 1325-1334.
73. Chaitman BR, Ho AP, Behm MO, et al. A randomized, placebo-controlled study of the effects of telcagepant on exercise time in patients with stable angina. Clin Pharmacol Ther 2012; 91: 459-466.
74. Sacco S, Bendtsen L, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain 2019; 20: 6.
75. Ray JC, Allen P, Bacsi A, et al. Inflammatory complications of CGRP monoclonal antibodies: a case series. J Headache Pain 2021; 22: 121.
76. Al-Hassany L, Goadsby PJ, Danser AHJ, MaassenVanDenBrink A. Calcitonin gene-related peptide-targeting drugs for migraine: how pharmacology might inform treatment decisions. Lancet Neurol 2022; 21: 284-294.

PEER REVIEWED FEATURE 1.5 CPD HOURS



Chronic migraine and other types of daily headaches

RICHARD J. STARK AM, MB BS, FRACP, MACLM
JASON C. RAY MB BS, FRACP, PhD
ELSPETH J. HUTTON MB BS, BMedSci(Hons), FRACP

Chronic daily headache is a common and disabling condition. It is usually due to primary headache, most often migraine, but other causes must be kept in mind. A simple approach to diagnosis is required.

Chronic daily headache is a common issue for people in Australia, with an estimated prevalence of 4% of the population.[1] For most people living with daily headaches, the cause is due to a primary headache disorder, with chronic migraine being the most common cause; however, several unique conditions should be considered in this patient group.

The nomenclature here can be confusing – in every other aspect of medicine 'chronic' refers to the length of time that a condition has been present. Neurologists, in something of an obstinate move, use 'chronic' in the *International Classification of Headache Disorders,* 3rd edition (ICHD-3) to refer to a headache disorder where the attacks occur on more than half of the days of a month (i.e. episodic migraine is 0 to 14 migraine days per month, and chronic migraine is ≥15 days per month).[2] The term 'chronic daily headache', therefore, is not actually a distinct diagnostic entity, and something of a tautology.

MedicineToday 2025; 26(7 Suppl): 16-21
First published in Medicine Today 2013; 14(1): 29-35
Updated July 2025

Professor Stark is a Neurologist in the Neurology Department, The Alfred Hospital, Melbourne; and Adjunct Clinical Professor in the Department of Neuroscience, Monash University, Melbourne. Dr Ray is a Neurologist in the Department of Neurology, Alfred Health and in the Department of Neurology, Austin Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne. Dr Hutton is a Neurologist in the Department of Neurology, Alfred Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne, Vic.

KEY POINTS

- Chronic daily headache is a common condition.
- Establishing the presence of chronic daily headache requires documentation of 15 days or more per month of prolonged headache (lasting more than four hours).
- Most cases of chronic daily headache are due to primary headache, but other causes such as structural lesions must be considered; most cases of primary headache that are troublesome are due to chronic migraine.
- Treatments for patients with chronic migraine are now available.
- Medication overuse is a common complication of headache treatment and makes successful treatment more difficult.

The diagnostic approach to a patient with chronic daily headache, however, is relatively simple (Flowchart). After establishing the presence of daily headaches, and consideration of secondary causes, ask the patient to identify the presence of migrainous, or cranial autonomic symptoms, which will help narrow the focus.

- The location of the pain: paying specific attention to if the headache is strictly side-locked (does not cross the midline).
- Migrainous features: presence of bilateral photophobia, phonophobia, nausea and vomiting. Apparent worsening of pain by exertion.
- Cranial autonomic symptoms: assess specifically if occurring on the same side as a side-locked headache (eye redness, tearing, nasal congestion, rhinorrhoea, eyelid oedema, ptosis and facial sweating). Note that photophobia may be present also, and curiously is often unilateral and ipsilateral.[2,3]

1. DIAGNOSTIC CRITERIA OF HEMICRANIA CONTINUA[2]

Description

Persistent, strictly unilateral headache, associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and/or with restlessness or agitation. The headache is absolutely sensitive to indomethacin.

Diagnostic criteria

A. Unilateral headache fulfilling criteria B to D

B. Present for >3 months, with exacerbations of moderate or greater intensity

C. Either or both of the following:

- at least one of the following symptoms or signs, ipsilateral to the headache:
  - conjunctival injection and/or lacrimation
  - nasal congestion and/or rhinorrhoea
  - eyelid oedema
  - forehead and facial sweating
  - miosis or ptosis
- a sense of restlessness or agitation, or aggravation of the pain by movement

D. Responds absolutely to therapeutic doses of indomethacin

E. Not better accounted for by another ICHD-3 diagnosis

Abbreviation: ICHD-3 = International Classification of Headache Disorders-3.

Primary headache disorders

Hemicrania continua

Hemicrania continua is an uncommon disorder with an estimated prevalence of 2.2 cases per 100,000 people but is very characteristic in its classic form (Box 1).[4] The headache is strictly unilateral in location and present daily and continuously, without pain-free periods. The pain is usually moderate to severe in intensity, and often located in the anterior temporal or retro-orbital area. It is unique (along with paroxysmal hemicrania) as one of two headache disorders that responds dramatically to treatment with indomethacin at high dose, but not other NSAIDs. A diagnostic trial of indometacin can therefore be informative, if there is clinical suspicion.

Cranial autonomic symptoms such as conjunctival injection or lacrimation, nasal congestion and ptosis or miosis are common when the pain is more severe and intermittent jabs or jolts of pain may be superimposed over the persistent headache. It can occur at any age; however, the mean age of diagnosis is 47.1 years and it is more common in women (2.8:1, female to male ratio).[4] In most patients the condition is unremitting.

The first-line treatment of patients with hemicrania continua is with indomethacin, but the doses required are often high (often 150 mg/day; sometimes 225 mg/day in divided doses). This means that gastric, renal and other side effects can limit its use.

New daily persistent headache

New daily persistent headache (NDPH) has an estimated prevalence of 0.03 to 0.1% in the general population, with an increased prevalence in adolescents than in adults.[5] Correct diagnosis has both therapeutic and prognostic implications because patients with this condition generally respond less well to many preventive strategies, and can be refractory to treatment. The major diagnostic pointer is that the patient can give the date of onset of the headache with considerable precision. The overall phenotype of a patient's headache may have migrainous or tension-type features (Box 2), which helps guide initial choices of therapy to medications that are more efficacious for either condition.

Most patients (53%) report no trigger for NDPH; however, in those with an identifiable trigger, the most common causes are a flu-like illness (22%), stressful life event (9%) and surgical procedures (9%).[5]

There appears to be two subtypes of NDPH: a self-limiting form, with 66% of patients achieving headache freedom by 24 months; and a refractory form, which is often resistant to aggressive preventive strategies, and can be challenging to treat.[5]

2. DIAGNOSTIC CRITERIA OF NEW DAILY PERSISTENT HEADACHE[2]

Description

Persistent headache, daily from its onset, which is clearly remembered. The pain lacks characteristic features, and may be migraine-like or tension-type-like, or have elements of both.

Diagnostic criteria

A. Persistent headache fulfilling criteria B and C

B. Distinct and clearly-remembered onset, with pain becoming continuous and unremitting within 24 hours

C. Present for >3 months

D. Not better accounted for by another ICHD-3 diagnosis

Abbreviation: ICHD-3 = International Classification of Headache Disorders-3.

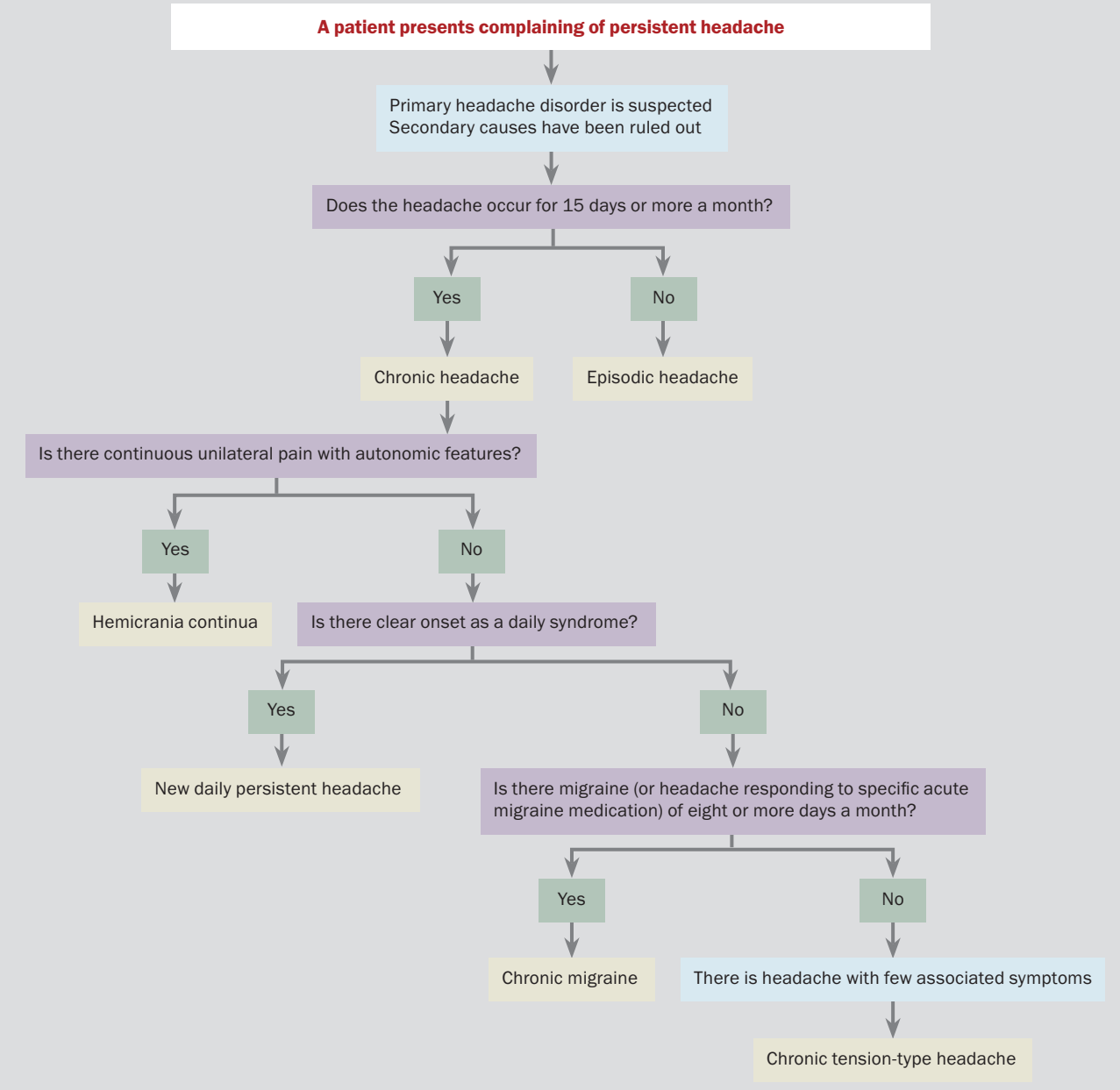
Chronic migraine

As the second leading cause of years lived with disability, chronic migraine may be the most important cause of chronic daily headache. Chronic migraine is defined as a patient who experiences headaches on 15 days or more per month for more than three months, which, on at least eight days per month, has the features of migraine (Box 3).[2,6] It has a global prevalence of 1 to 5%.[7]

The definition of chronic migraine has evolved amid some controversy. The problem is that as migraine becomes more frequent, the characteristic features (i.e. nausea, vomiting, light and sound sensitivity and throbbing) may become less prominent. The definitions of chronic migraine do not require that all headache episodes be migrainous, but various attempts have been made to set out the minimum requirement. Practically, if a patient with chronic daily headache has evolved gradually from a previous diagnosis of migraine, it is likely to be evolution of the disease, even if the patient does not quite meet the eight migraine days per month outlined in the diagnostic criteria.

Although their headaches are not always migrainous, patients with chronic

DIAGNOSING THE PATIENT WITH PERSISTENT HEADACHE



migraine are much more disabled than those with episodic migraine. The inability to commit reliably to routine work or domestic and social activities because of headache present most days is often the most disturbing issue for patients. Attempts to continue to function by taking escalating doses of acute medication may help in the short term but tend to produce intractable chronic migraine complicated by medication overuse.

Most cases of chronic migraine evolve from a pattern of episodic migraine. It is therefore sensible to look at the risk factors that contribute to this conversion (Box 4).

The single most important issue when presented with a patient with increasing frequency of migraine (especially if they are approaching the chronic migraine range with a frequency of almost 15 days per month) is to avoid overusing acute treatments that are known to produce medication overuse

3. DIAGNOSTIC CRITERIA OF CHRONIC MIGRAINE[6]

A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B to D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*

C. On ≥8 days/month for >3 months, fulfilling any of the following:
- criteria C and D for 1.1 *Migraine without aura*
- criteria B and C for 1.2 *Migraine with aura*
- believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis

Abbreviation: ICHD-3 = International Classification of Headache Disorders-3.

headache. These include, either individually or in combination:
- triptans: should use less than 10 days per month
- simple analgesia (paracetamol or NSAIDs): should use less than 15 days per month
- opiates or combination analgesics: generally not recommended, or use less than 10 days per month.

Starting effective preventive therapy is a key modifiable factor that impacts progression. Preventive treatments for migraine, including chronic migraine, are discussed in the article on 'Migraine in 2025: an update on management' elsewhere in this *Focus on headache* supplement. If there is a component of medication overuse headache, withdrawing the offending medication in combination with preventive therapy can be effective (see article on 'Medication overuse headache: less is MOH', included in this *Focus on headache* supplement).

Concomitant medical and psychiatric disorders, including depression, sleep disorders and obesity, should be managed at the same time as the chronic migraine. Patients with a susceptibility to migraine may have migrainous headaches triggered by other painful conditions around the head and neck and, if present, these should also be treated; however, some patients invest substantial effort in pursuing unrewarding treatments of the neck, temporomandibular joint, sinuses and so forth.

Although challenging, the treatment of patients with chronic migraine can be enormously rewarding. Patients who can once more engage reliably in work and family and social activities are among the most grateful patients seen in neurological practice.

Chronic tension-type headache

Chronic tension-type headache is defined as chronic daily headache that fails to meet the criteria for the other three disorders discussed, namely hemicrania continua, NDPH and chronic migraine. It is often described as a featureless band of pain. Chronic tension-type headache is somewhat controversial as an entity as many US headache specialists believe that it is over diagnosed and is in fact rare: they point to the fact that when diary data are collected, many diagnoses of tension-type headache should in fact be migraine.[8] In Europe, there is a different view, and tension-type headache is considered common. It does seem clear, however, that chronic tension-type headache is much less disabling than chronic migraine.

Despite its apparent frequency (up to 2% of the population in many surveys), the treatment of patients with chronic tension-type headache is not well defined.[1] There have been few trials addressing this. There is some evidence to support the use of amitriptyline in doses of 10 to 75 mg/day (off-label use).[9]

Secondary headaches that can produce a pattern of chronic daily headache

Although most patients with chronic daily headache have a primary headache with no obvious structural or other cause, some specific conditions that may cause headache should be considered. Pain arising from the neck, sinuses or eyes is usually diagnosed easily. The following conditions also deserve attention.

4. RISK FACTORS FOR MIGRAINE PROGRESSION FROM EPISODIC TO CHRONIC MIGRAINE

Not modifiable by health interventions
- Female sex
- Low socioeconomic status
- Head trauma

Modifiable by health interventions
- Obesity
- Medication overuse
- Caffeine overuse
- Stressful life events
- Snoring

Medication overuse headache

Medication overuse headache is a significant health issue, affecting one-quarter of patients with migraine, and up to 70% of patients in specialist clinics and with chronic daily headache.[10] The mechanism seems to be that regular use of the offending agent results in a degree of physiological habituation. Absence of the agent can produce a withdrawal effect, the most prominent feature of which (in a headache-prone individual) is recurrent headache. This is sometimes described as rebound headache and some patients find this term helpful in understanding the condition; however, it is important to recognise that this habituation or sensitisation of pain circuits in the brain also occurs in patients who do not experience rebound headaches.

Making a diagnosis of medication overuse headache is not difficult: it simply requires an accurate history of medication use. This is often best approached by asking how many days in a month there is no medication taken by the patient for headache.

The traditional approach to the treatment of patients with medication overuse headache has involved abrupt withdrawal of the agent in question. However, it is certainly reasonable to counsel patients on the importance of eliminating such medications and to offer migraine prophylaxis to allow them to wean off the offending drug gradually, although, in practice, few patients achieve this.

Abrupt withdrawal is also difficult as it requires fortitude and commitment from the patient who must obviously see the point and want treatment. Even when the overused agent is an opioid, most patients are keen to stop taking it because their dependence on the drug has no recreational element. Naturally, such abrupt withdrawal inevitably causes a severe headache that must be managed in some other way. Outpatient protocols include the use of NSAIDs (e.g. naproxen sustained release 750 mg daily for a week) or corticosteroids (e.g. prednisolone 60 mg/day for a week and then taper). Inpatient treatment excludes the patient from day-to-day responsibilities and allows for a wider range of options to control headache, including dihydroergotamine or lignocaine by infusion. Severe withdrawal headaches often settle within two to four days for triptan overuse, four to seven days for ergotamine overuse and seven to 10 days for substantial codeine overuse. The withdrawal phase must be followed by a plan to manage breakthrough headaches without reverting to the offending drugs. Medication overuse headache is discussed in more detail in the article on 'Medication overuse headache: less is MOH', included in this *Focus on headache* supplement.

Intracranial structural lesions

Space-occupying lesions such as tumours may present with headache as the primary complaint. For a lesion to become so large as to cause raised intracranial pressure without obvious focal signs, it must reside in a 'silent area' of the brain (an area not likely to produce obvious physical signs), such as the frontal lobes and anterior temporal lobes. Lesions near the third ventricle, aqueduct or fourth ventricle may be smaller but cause hydrocephalus through ventricular obstruction. Typically, headache caused by raised intracranial pressure is said to be worse in bed or on waking, but this feature is not reliable. Most mass lesions produce a gradually progressive increase in symptoms over weeks or months. Often a careful neurological examination will show abnormalities such as papilloedema or focal signs. Modern imaging, especially MRI, is excellent at revealing such problems and should be performed if there is any suspicion of a space-occupying lesion.

Idiopathic intracranial hypertension

Formerly called benign intracranial hypertension or pseudotumour cerebri, idiopathic intracranial hypertension typically occurs in overweight young women. Diagnostic clues include symptoms of transient visual obscuration (darkening of vision in one eye) on rising from a stooped position, pulsatile tinnitus, diplopia (from partial sixth nerve palsy) and the finding of papilloedema. Imaging is typically normal, but cerebrospinal fluid pressure measured by lumbar puncture is high.

Idiopathic intracranial hypertension is an important diagnosis to make because neglecting the condition may result in severe visual loss from prolonged papilloedema. Treatment includes weight loss and acetazolamide, which is typically commenced at 500 mg twice per day, and advanced as required or tolerated to 2 to 4 g per day. Surgery (such as optic nerve sheath fenestration or shunting) may be required in refractory cases to save the patient's vision. The pathogenesis is complex but an important mechanism contributing to persistent raised pressure is dynamic narrowing of venous sinuses: the elevated intracranial pressure compresses the sinuses, causing obstruction to venous outflow and thus even higher pressures. This vicious cycle can be addressed by stenting the offending sinus (identified by venography) but the long-term pros and cons of this technique are debated.[11]

Low-pressure headache

Leakage of cerebrospinal fluid from the dural sac can cause headache. This is a well-known condition after lumbar puncture (or when the dura is accidentally punctured in an epidural injection or infusion), when postural headache (present soon after rising and relieved by lying down) is the obvious clue. It is less well known that a similar headache may occur spontaneously. This is usually caused by leakage of cerebrospinal fluid from a nerve root sleeve in the spine. The headache often appears over a day or two (similar to NDPH) and has the expected postural features.

MRI scanning of the brain, with contrast, shows a number of characteristic features (including prominent enhancement of the dura) but they may be subtle and not recognised if the clinical suspicion of low cerebrospinal fluid pressure has not been conveyed to the radiologist. Locating the leak in the spine may be difficult and again it is vital to liaise with the radiologist to obtain the best results. Post-lumbar puncture headache that does not resolve promptly usually responds well to epidural autologous blood patch. Similar techniques can be used in patients with spontaneous low-pressure headache if the site of the leak can be identified.

Giant cell arteritis

Giant cell arteritis typically occurs after 55 years of age. It presents with nonspecific headache (and often diffuse malaise and muscular pain from associated polymyalgia rheumatica). Erythrocyte sedimentation rate and C-reactive protein levels are usually markedly elevated and are useful screening tests. The diagnosis should be confirmed by temporal artery biopsy; however, treatment should not

be delayed until the biopsy in cases of strong clinical suspicion. The diagnosis is important because of the risk of blindness from retinal artery occlusion if untreated. In selected patients, glucocorticoid-sparing agents such as tocilizumab are considered.

Conclusion

Chronic daily headache is a common and debilitating disorder. Accurate diagnosis is not difficult in most cases. Modern approaches to treatment, with recognition of medication overuse and active management of chronic migraine, may provide substantial relief to many patients. Helping patients with such a disabling condition to improve their quality of life is very rewarding. MT

References

1. Pascual J, Colas R, Castillo J. Epidemiology of chronic daily headache. Curr Pain Headache Rep 2001; 5: 529-536.
2. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders. 3rd ed. Cephalalgia 2018; 38: 1-211.
3. Irimia P, Cittadini E, Paemeleire K, Cohen AS, Goadsby PJ. Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. Cephalalgia 2008; 28: 626-630.
4. Hagan K. One-year prevalence of cluster headache, hemicrania continua, paroxysmal hemicrania and SUNCT in Norway: a population-based nationwide registry study. J Headache Pain 2024; 25: 30.
5. Yamani N, Olesen J. New daily persistent headache: a systematic review on an enigmatic disorder. J Headache Pain 2019; 20: 80.
6. Headache Classification Committee; Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 2006; 26: 742-746.
7. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia 2010; 30: 599-609.
8. Lipton RB, Cady RK, Stewart WF, Wilks K, Hall C. Diagnostic lessons from the spectrum study. Neurology 2002; 58(9 Suppl 6): S27-S31.
9. Lance JW, Curran DA. Treatment of chronic tension headache. Lancet 1964; 1: 1236-1239.
10. Fischer A, Jan A. Medication-overuse headache. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
11. Ahmed RM, Wilkinson M, Parker GD, et al. Transverse sinus stenting for idiopathic intracranial hypertension: a review of 52 patients and of model predictions. AJNR 2011; 32: 1408-1414.

COMPETING INTERESTS: Professor Stark has served on advisory boards for Teva, Eli Lilly, AbbVie, Viatris and Lundbeck; and received payment for educational presentations from AbbVie, Teva, Eli Lilly and Viatris. Dr Ray has received honoraria for educational presentations for AbbVie, Novartis and Viatris; has served on medical advisory boards for Pfizer, Viatris and Lilly; and his institution has received funding for research grants, clinical trials and projects supported by the International Headache Society, Brain Foundation, Lundbeck, AbbVie, Pfizer and Aeon. Dr Hutton has served on advisory boards for Sanofi-Genzyme, Novartis, Teva, Eli Lilly, Allergan, Lundbeck, been involved in clinical trials sponsored by Novartis, Teva, Xalud and Cerecin, and has received payment for educational presentations from Allergan, Teva, Eli Lilly and Novartis.

Episodic migraine in women

ELSPETH J. HUTTON BMedSci(Hons), MB BS, FRACP, PhD
SHULI CHENG MB BS, FRACP
RICHARD J. STARK AM, MB BS, FRACP, FANZAN, MACLM

Hormonal changes experienced by women at various stages of life can affect the frequency and duration of migraine. Treating pregnant or breastfeeding women with migraine can pose a challenge for GPs.

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KEY POINTS

- There are significant associations between migraine activity and hormonal fluctuations throughout a woman's life.
- Migraine with aura increases the risk of stroke from a very low baseline in women of childbearing age. Smoking and use of oral contraceptives both increase the risk further. In any individual, the risks must be balanced against the benefits of taking the oral contraceptive pill.
- Treatment options for menstrual migraine include standard acute and prophylactic treatments, hormonal manipulation and short-term prophylactic regimens at the vulnerable time ('mini-prophylaxis').
- Migraine may worsen or improve in the first trimester, but generally improves significantly for the remainder of the pregnancy.
- Management of migraine during pregnancy is difficult because of warnings about the use of many relevant drugs during pregnancy and lactation.

Migraine is a common neurological disorder affecting about 17% of women and 6% of men. It is characterised by episodic disabling headaches, with the features outlined in Box 1.[1] The onset of migraine increases from the first to fourth decade of life and then declines, with the prevalence in postmenopausal women falling to a similar rate to that in men. There are significant associations between migraine activity and hormonal fluctuations throughout the life of a women such as at menarche, during menstruation, during pregnancy, when breastfeeding and during the postpartum period, during perimenopause, at menopause and when using hormonal modulators, such as the oral contraceptive pill (OCP) and menopausal hormone therapy (MHT).

These factors should be considered in the assessment of women with migraine, because they may help target more effective treatment strategies.

Migraine and cardiovascular risk

The cardiovascular risk of OCP use in women with migraine is a common concern for practitioners treating young women with migraine. This risk must be considered bearing in mind that the baseline incidence of stroke is low in young women, which means that any increase in relative risk is a minimal increase in an individual's absolute risk for stroke. The incidence of stroke varies with gender and ethnicity, but is about 4.5 per 100,000 women aged 25 to 35 years, compared with about 200 per 100,000 in the general population.[2] In five meta-analyses, the relative risk for ischaemic stroke varied between 1.56 and 2.41 for migraine with aura, and between 1.02 and 1.83 for migraine without aura compared with those without migraine.[3] There is an increased risk of angina, myocardial infarction and cardiovascular death, especially with migraine with aura.[3] Furthermore, increases in risk

MedicineToday 2025; 26(7 Suppl): 22-26
First published in Medicine Today 2013; 14(2): 42-48
Updated July 2025

Dr Hutton is a Neurologist in the Department of Neurology, Alfred Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne. Dr Cheng is a Neurologist in the Neurology Department, The Alfred Hospital, Melbourne. Professor Stark is a Neurologist in the Neurology Department, The Alfred Hospital; and Adjunct Clinical Professor in the Department of Neuroscience, Monash University, Melbourne, Vic.

were seen in women older than 45 years of age, smokers and those on the OCP.[4] Men with migraine have a relative risk for cardiovascular disease of 1.24 (95% confidence interval, 1.0 to 1.5).[5]

In addition to stroke and acute myocardial ischaemia, patients with migraine are at increased risk for peripheral vascular disease (claudication) and retinal microvascular disease. The underlying biology of these associations remains unclear and is further clouded by an association between migraine and the metabolic syndrome (obesity, hypertension, hyperlipidaemia and insulin resistance).

The background cardiovascular risk in young women is relatively low, so the presence of migraine is not an absolute contraindication to OCP use. Rather, careful individual assessment of risk is important when considering the risk of OCP use, with evaluation of the patient's overall cardiovascular risk including body mass index, lipid profile, blood pressure, age, presence of insulin resistance and smoking status (Box 2). Due to an increased thrombotic risk, the use of the combined OCP is at least relatively contraindicated in women with migraine who are smokers, are over the age of 35 years, have other cardiovascular risk factors or valvular heart disease, or have migraine with aura. The level of concern increases considerably when a combination of these factors is present. Ultimately, in any individual, the risks must be balanced against the benefits of taking the OCP.

Menstrual migraine

Migraine may be associated with menses, either occurring only at this time or with increased frequency and severity from two days before to three days after the onset of menses. Pure menstrual migraine is defined by the International Headache Society as migraine attacks occurring exclusively on day one of menstruation (± two days) in at least two out of every three menstrual cycles and at no other times of the cycle.[1] A headache diary recording the menstrual cycle is often crucial in identifying women with menstrually-related migraines or pure menstrual migraine. Sixty percent of women have an increased frequency of migraine perimenstrually, whereas 14% have migraine exclusively in this period (true menstrual migraine). The trigger is the drop in oestrogen levels in the luteal phase of the menstrual cycle (Figure); however, no increase in migraine frequency is associated with the drop in oestrogen at ovulation. Studies have demonstrated that a persistent elevation in oestrogen levels for several days followed by a drop in levels is needed to trigger a migraine in susceptible individuals. In many patients, triggers are cumulative, so particular attention to good sleep and avoiding other triggers such as stress, alcohol and missed meals at the time of menses may be useful.

Pharmacological treatment for women with menstrual migraine, as for those with other types of migraine headache, may be acute or preventive, with the decision of which mode to employ being guided by the severity and frequency of the migraines and the patient's response to treatment.

1. KEY MIGRAINE FEATURES AND DEFINITIONS[1]

Key features

At least five attacks fulfilling the following characteristics are required for a diagnosis of migraine

Pain characterised by at least two of the following:

- Unilateral location
- Moderate or severe pain intensity
- Pulsating quality
- Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

Associated symptoms include at least one of the following:

- Photophobia and phonophobia
- Nausea and/or vomiting

Duration of attacks

- Four to 72 hours (untreated or unsuccessfully treated)

Other key features

- Prodromes (in about 60% of cases, six to 48 hours prior)
  - fatigue, altered mood, heightened senses, yawning, food cravings, stiff neck, fluid retention, increased urination, altered bowel habit, feeling cold
- Postdrome (can persist for up to 48 hours)
  - feeling tired, difficulty with concentration, neck stiffness
- Aura (in about 20% of cases, evolves over five to 20 minutes, lasts up to 60 minutes)
  - commonly visual: enlarging scotoma with shimmering edge, stars, dots, wavy lines, zig zag lines, visual distortion
  - less commonly sensory: paraesthesia spreading from hand to ipsilateral shoulder or face over minutes
  - rarely: hemiplegia (can last longer than 60 minutes), speech disturbance, brainstem, retinal
  - all features are characterised by full resolution in one hour, mix of positive and negative symptoms and gradual development
  - can accompany or precede the headache phase

Definitions

- Episodic migraine: headache on fewer than 15 days per month
- Chronic migraine: headache on 15 days or more per month, with at least eight days per month with features of migraine headache, for more than three months
- Menstrually-related migraine: migraine typically occurring from two days before to three days after the onset of menses

Acute treatment options include the use of a triptan. There are many different agents on the market and patients often respond to some triptans better than others, perhaps due to variations in absorption. Therefore, failure of a patient to respond to one agent does not indicate that they will be resistant to other members of the drug class. For patients who are genuinely resistant to all drug classes, subcutaneous sumatriptan is often helpful and is probably

2. CARDIOVASCULAR RISK FACTORS IN MIGRAINE

The risk of cardiovascular disease, particularly stroke and acute myocardial infarction, increases in patients with migraine, particularly in older women and those with migraine with aura. The risk is, however, modulated by other modifiable risk factors. The overall risk must be considered in the decision about whether to prescribe the oral contraceptive pill to an individual.

Patient characteristics

- Migraine, especially migraine with aura
- Female
- Older age (over 35 years)

Modifiable risk factors

- Hypertension
- Dyslipidaemia
- Insulin resistance
- Obesity
- Smoker

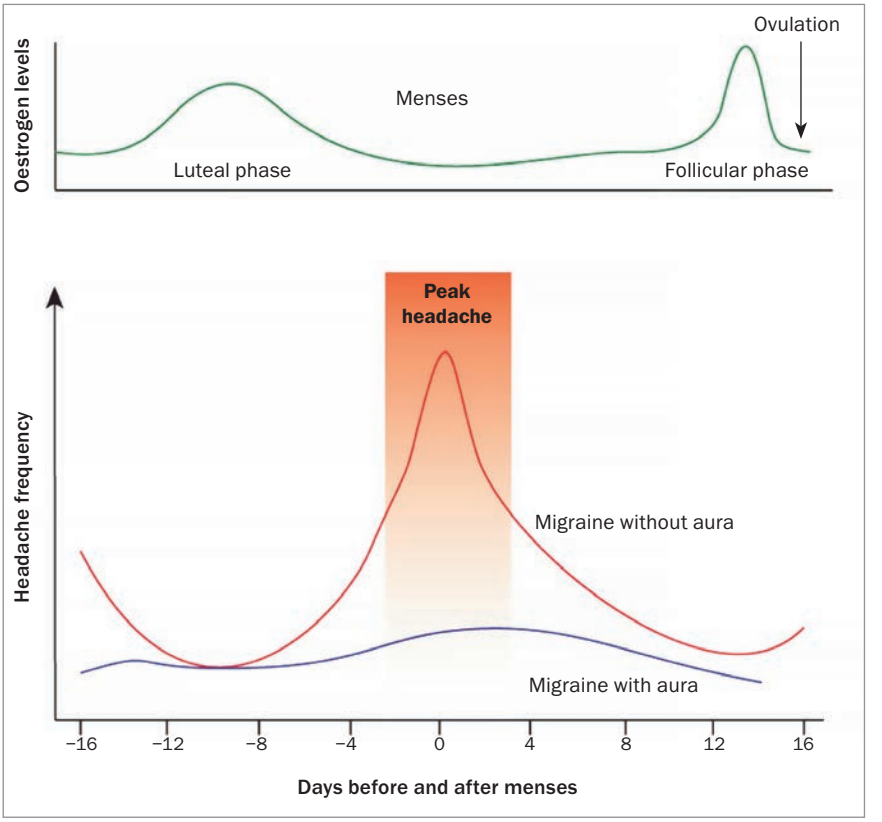


Figure. The relation between migraine frequency and the menstrual cycle. There is a stronger menstrual association for migraine without aura than migraine with aura. Note the typical increase in headache frequency from about two days before (day −2) to three days (day +3) after the start of menses (day 0). The lack of increase in migraine associated with the drop in oestrogen levels at ovulation is thought to be due to the need for several days of prolonged elevation of oestrogen prior to a fall in order to trigger migraine.

underused. Other acute treatment options include NSAIDs (e.g. aspirin 600 to 900 mg, ibuprofen 400 to 800 mg, naproxen 500 to 750 mg [as a single dose, repeated once or twice per day if required]), paracetamol and antiemetics.

Short-term prophylactic regimens ('mini-prophylaxis') may be structured to start two to three days before the start of menses and to continue for one to two weeks as needed. Benefit is seen with the use of a long-acting triptan, such as naratriptan 2.5 mg half a tablet twice a day, from three days before to three days after the onset of menses. Another option is naproxen 500 mg three times a day. The oral calcitonin gene-related peptide antagonist, rimegepant, is attractive as an option for mini-prophylaxis because of its long half-life and good side-effect profile. Evidence of its benefit is currently only anecdotal and, as it is not PBS funded, it is expensive. If a woman experiences frequent migraines at other times of the cycle, she should take a preventive agent, the dose of which may be increased perimenstrually if needed. (The choice of preventive agent would be made after considering other comorbidities, previous response and previous adverse reactions to preventives.)

Modulation of migraine by hormonal factors, including OCP use, should be carefully evaluated using a headache and menstruation diary. Both the combined OCP and the progesterone-only pill may ameliorate or worsen migraine headaches, and the effect must be assessed on an individual basis. In addition, the risk of OCP use itself must be considered. In women at lower risk for cardiovascular disease, the risk of OCP use may be minimised by using a low-oestrogen OCP (e.g. a preparation containing 20 mcg ethinyloestradiol). The progesterone-only pill and contraceptive implants do not carry any increased risk of thrombotic disease and may reduce migraine frequency and severity. Some patients with menstrual migraine respond to elimination of the placebo days by continuous cycling (with one withdrawal bleed every three months) and use of one of the mini-prophylactic regimens during the pill-free days. Starting an OCP purely to manage migraine would not be recommended; however, it may be used to maximise benefit and minimise risk in women requiring an OCP for other reasons. Polycystic ovary syndrome and endometriosis confers a different risk–benefit profile.

Migraine in pregnancy

Migraine may worsen or improve in the first trimester, but generally improves significantly for the remainder of the pregnancy. The greatest improvement occurs

in women with menstrual migraine or those in whom migraine commenced at menarche. One-quarter of women will not notice any change in migraine frequency during pregnancy. Persistent headaches at the end of the first trimester are associated with a lack of improvement in migraine for the remainder of the pregnancy.

Women with migraine have a greater risk of pregnancy-induced hypertension and pre-eclampsia, as well as other vascular events in pregnancy and peripartum. There is a higher risk of pregnancy-related ischaemic stroke in women with migraines, with an odds ratio of 16.9, on a background risk of about 34 per 100,000 deliveries.[6] A population-based cohort study in Denmark showed increased risks of low birthweight, preterm birth, caesarean section delivery, neonatal dispensings, respiratory distress syndrome and febrile seizures (adjusted prevalence ratio 1.2) in women with migraine.[7]

Other causes of headache in pregnancy must always be considered, including venous sinus thrombosis, pre-eclampsia, stroke, brain tumour, arteriovenous malformation and idiopathic intracranial hypertension. These should be considered particularly in women with new-onset headache, or new aura or a substantial change in their headache phenotype during pregnancy. The preferred method of neuroimaging in pregnant women is MRI, although the use of gadolinium is discouraged because of the limited evidence concerning short- and long-term fetal outcomes, particularly in first trimester use.

The management of women with migraine during pregnancy is difficult because most of the drugs used to treat migraine at other times have warnings about their use in pregnancy and lactation listed in the prescribing information. This leaves the clinician in a dilemma about whether or not to prescribe the drugs; an individual patient's symptoms may be of such severity that intervention is considered essential despite some risk. In every case, the potential benefits must be balanced against the potential risks.

Migraine prophylaxis should ideally be optimised before conception, with a focus on using the safest agents. The use of nonpharmacological techniques such as relaxation, massage, acupuncture, regular exercise, adequate sleep and avoidance of triggers should be encouraged.[8] Smoking cessation should also be reinforced, for a variety of health reasons, including reduced headache severity. If possible, women should be weaned off continuous preventives before conception or, if this is not possible, treatment switched to one of the safer prophylactic agents. Supplements such as magnesium 200 to 300 mg twice a day and coenzyme Q10 200 mg a day are likely safe, whereas the safety of riboflavin is less proven. Feverfew should be avoided, as it can induce uterine contractions and spontaneous abortion. Iron deficiency can increase migraine frequency, severity and duration, particularly in women with menstrually-related migraine, and screening and replacement should be considered.

Safer pharmacological options include beta blockers (although they should be tapered four weeks before delivery and their use is associated with a possible risk of growth retardation, especially with atenolol,[9] and of fetal and newborn bradycardia) and calcium channel blockers (usually verapamil). Although antidepressants such as amitriptyline and venlafaxine have a lower TGA pregnancy rating (categories C and B2, respectively), they can be highly effective preventives, and have extensive clinical experience of use in pregnancy. They would therefore generally be used ahead of agents such as gabapentin, despite its B1 rating. Other anticonvulsants, particularly topiramate and sodium valproate, should be avoided.

For patients with chronic migraine, there is now some reassuring evidence that onabotulinumtoxinA carries very low risk in pregnancy.[10] It may be a very useful option especially when a woman is trying to conceive. Calcitonin gene-related peptide antibodies are not established as safe in pregnancy, and because of their long half-lives need to be withdrawn about five months before conception is attempted.

A particularly difficult time may occur when a woman is trying to conceive. During this time, prophylaxis will usually have been ceased to avoid teratogenesis, but conception may not occur at once, especially in women who used the OCP for contraception. To increase a woman's chances of achieving a quick conception, a switch from the OCP to barrier contraceptive methods for two or three months before ceasing prophylaxis may be of value.

Options for the treatment of pregnant women with acute migraine include paracetamol 1 g plus metoclopramide 10 mg or, during the second trimester only, NSAIDs. NSAIDs should be avoided in the first trimester because of concerns about an association with miscarriage and in the third trimester because of the risk of premature closure of the ductus arteriosus and oligohydramnios. Triptans may be used to treat pregnant women with moderate to severe migraine symptoms. There is a theoretical risk of uteroplacental vasoconstriction and increased uterotonic activity with their use, but pregnancy registers of sumatriptan (category B3) use are reassuring; sumatriptan is also considered safe to use when breastfeeding. Antiemetics such as prochlorperazine and ondansetron may be helpful both to treat nausea and for their antimigraine effects. Opiates may be used if a woman's symptoms are severe, but carry a greater risk of inducing medication-overuse headache, as well as a risk of neonatal withdrawal if used near term. Women with prolonged migraines may require intravenous hydration and consideration of magnesium sulfate (1 g intravenous) or high-dose oral prednisolone (up to 75 mg a day for two days) or bilateral greater occipital nerve blocks. Ergotamines are absolutely contraindicated in pregnancy.

Migraine and breastfeeding

Half of women with migraine experience recurrence of headache in the first month postpartum. Most of these will be migraine, but it is worth noting that increased risk

of reversible cerebral vasoconstriction syndrome and pre-eclampsia persist for six weeks postpartum.[11]

Breastfeeding may reduce headache incidence, but the data in this area are conflicting – certainly there is no evidence to suggest worsening of migraine in breastfeeding women.[12]

During breastfeeding, paracetamol, ibuprofen and sumatriptan may be used acutely. Aspirin is not to be used. Magnesium, riboflavin, beta blockers and verapamil also appear to be safe during breastfeeding. Cyproheptadine and ergotamine should be avoided.

Migraine in the perimenopausal period

The prevalence of migraine decreases with increasing age; however, menopause may increase, decrease or have no effect on migraine frequency. Surgical menopause is more likely to worsen migraine than natural menopause, presumably due to the rapidity of hormonal flux. Evaluation of migraine symptoms should be part of the assessment of menopausal symptoms in all women. When considering the use of MHT, it is useful to know that the oestrogen component of MHT may also worsen migraine, particularly at higher doses or with varying blood levels. This may be minimised by administering continuous, rather than cyclical, MHT, as well as the lowest effective dose of oestrogen by a nonoral route, to achieve more even blood levels. It appears that the transdermal application of hormone therapy is not associated with risk of stroke.[13]

Other pharmacological agents with evidence for efficacy in both migraine prophylaxis and reduction of hot flushes include the serotonin selective reuptake inhibitors (e.g. fluoxetine and venlafaxine [off-label use]) and gabapentin.

Conclusion

In all women, standard principles of migraine treatment apply. Women with infrequent headaches with a good response to acute treatment may be managed with intermittent acute therapies. Women with headaches occurring on more than four to five occasions per month may benefit from the addition of a preventive agent. Use of acute migraine treatments (triptans and NSAIDs) should be limited to two to three days a week to reduce the risk of transformation to chronic migraine and acute medication overuse.

Hormonal considerations in women may suggest the use of mini-prophylaxis around the time of menses, as well as guiding decisions about OCP use and awareness of the possible exacerbation of migraine perimenopausally. Prepregnancy counselling and planning in women with migraines is also of great importance.

Lifestyle factors remain important in the management of migraine in women, with the focus on limiting variations in daily routine that may trigger migraine. These include ensuring regular adequate sleep, regular healthy meals, identification and avoidance of any potential food triggers, avoidance or moderation of alcohol use, regular moderate exercise and the use of relaxation and stress management techniques. MT

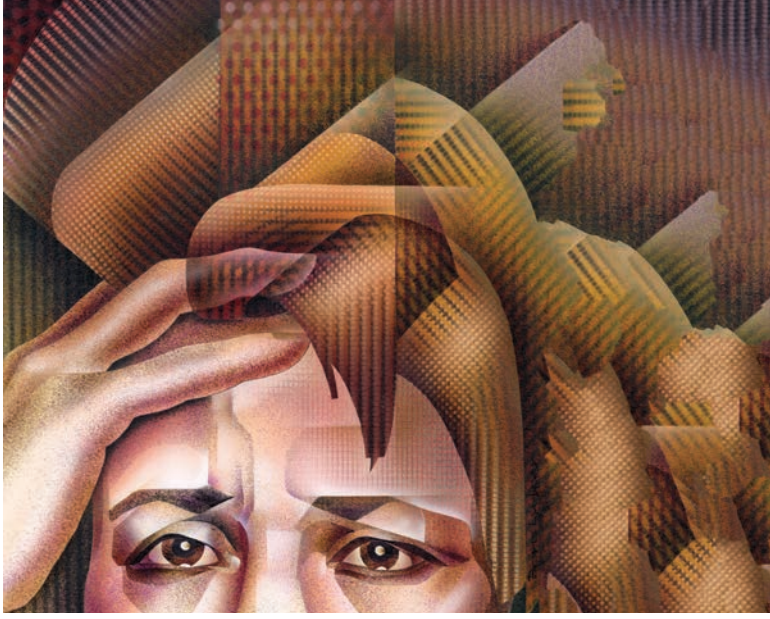
References

1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd ed. Cephalalgia 2018; 38(Suppl 1): 1-211.
2. Putaala J, Metso AJ, Metso TM, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. Stroke 2009; 40: 1195-1203.
3. Kalkman D, Couturier E, Bouziani A, et al. Migraine and cardiovascular disease: what cardiologists should know. Eur Heart J 2023; 44: 2815-2828.
4. MacClellan LR, Giles W, Cole J, et al. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. Stroke 2007; 38: 2438-2445.
5. Kurth T, Gaziano J, Cook NR, et al. Migraine and risk of cardiovascular disease in men. Arch Intern Med 2007; 167: 795-801.
6. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol 2005; 106: 509-516.
7. Skajaa, N, Szepligeti S, Xue F, et al. Pregnancy, birth, neonatal and postnatal neurological outcomes after pregnancy with migraine. Headache 2019; 59: 869-879.
8. Mauskop A. Nonmedication, alternative, and complementary treatments for migraine. Continuum (Minneap Minn) 2012; 18: 796-806.
9. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens 1999; 12: 541-547.
10. Wong HT, Khan R, Buture A, Khalil M, Ahmed F. OnabotulinumtoxinA treatment for chronic migraine in pregnancy: An updated report of real-world headache and pregnancy outcomes over 14 years in Hull. Cephalalgia 2025; 45: 3331024251327387.
11. Burch R. Epidemiology and treatment of menstrual migraine and migraine during pregnancy and lactation: a narrative review. Headache 2020; 60: 200-216.
12. Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M. Headache and migraine during pregnancy and puerperium: the MIGRA-study. J Headache Pain 2011; 12: 443-451.
13. Lokkegaard E, Nielsen L, Keidine N. Risk of stroke with various types of menopausal hormone therapies: a national cohort study. Stroke 2017; 48: 2266-2269.

COMPETING INTERESTS: Dr Hutton has served on advisory boards for Sanofi-Genzyme, Novartis, Teva, Eli Lilly, Allergan, Lundbeck, been involved in clinical trials sponsored by Novartis, Teva, Xalud, Cerecin, and has received payment for educational presentations from Allergan, Teva, Eli Lilly and Novartis. Dr Cheng has received lecture fees from Pfizer. Professor Stark has served on advisory boards for Teva, Eli Lilly, AbbVie, Viatris and Lundbeck; and received payment for educational presentations from AbbVie, Teva, Eli Lilly and Viatris.

Unusual primary headaches

Keys to an accurate diagnosis



ELSPETH J. HUTTON MB BS, BMedSci(Hons)
JASON C. RAY MB BS, FRACP, PhD
RICHARD J. STARK AM, MB BS, FRACP, MACLM

A patient presents to you with recurrent headaches that do not quite fit the pattern of migraine or tension-type headaches. Which disorders should you consider?

Most patients with headache have a primary headache disorder, with migraine and tension-type headache being the most common. Primary headache disorders are so common that even the less well known varieties will be seen occasionally in general practice: this paper addresses a number of these. Formal diagnostic criteria are published in the *International Classification of Headache Disorders* (3rd edition).[1] An approach to diagnosis and investigation to exclude causes of secondary headache is included as a separate paper in this collection.[2]

Trigeminal autonomic cephalgias

Trigeminal autonomic cephalgias (TACs) represent four conditions: cluster headache; short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache with cranial autonomic symptoms (SUNA); hemicrania continua; and paroxysmal hemicrania. A patient who experiences a TAC will typically report the 'three As':

- anterior, side-locked pain
- autonomic features
- a sense of internal agitation or restlessness during exacerbations.

MedicineToday 2025; 26(7 Suppl): 27-32
First published in Medicine Today 2013; 14(10): 27-44
Updated July 2025

Dr Hutton is a Neurologist in the Department of Neurology, Alfred Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne. Dr Ray is a Neurologist in the Department of Neurology, Alfred Health and the Department of Neurology, Austin Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne. Professor Stark is a Neurologist in the Neurology Department, The Alfred Hospital, Melbourne; and Adjunct Clinical Professor in the Department of Neuroscience, Monash University, Melbourne, Vic.

KEY POINTS

- Primary headache disorders other than migraine and tension-type headache are less well known; however, not all are rare and they will occasionally be encountered in general practice.
- The trigeminal autonomic cephalgias (TACs) are short-lasting headaches with prominent autonomic features and should be differentiated from short-lasting headaches without autonomic features.
- Photophobia and phonophobia are usually unilateral in TACs but are bilateral in migraine, even when the pain is lateralised.
- Autonomic symptoms in TACs tend to be lateralised to the side of the pain, prominent and consistent between attacks. In contrast, those in migraine are generally mild, bilateral and do not correlate with attack severity.
- The diagnosis of other recurrent primary headache disorders is often suggested by specific triggers (e.g. sexual activity, exertion, coughing) or distinctive pain characteristics (e.g. local, brief stabbing pain, or focal coin-shaped area of pain).

Autonomic features (which occur on the side of the headache) include:

- facial flushing, pallor or sweating
- redness, tearing or itchy/gritty sensation of the eye
- nasal congestion or rhinorrhoea
- drooping of the eyelid (ptosis), change in pupillary size (miosis), or Horner's syndrome
- ear fullness
- salivation.

Photophobia and phonophobia in TACs are usually unilateral, in contrast to the bilateral sensitivity seen in migraine.[3] Autonomic features in TACs are typically lateralised to the side of the pain, prominent and consistent between attacks, whereas in migraine they are generally milder, bilateral and not correlated with attack severity.

Subtypes of TACs can usually be distinguished by the cycle pattern and the length and frequency of the attacks (Table). Hemicrania continua and SUNCT/SUNA are easily distinguishable by the length of their attacks (continuous, and seconds, respectively). Cluster headache is differentiated from paroxysmal hemicrania by

TABLE. CLINICAL FEATURES AND TREATMENT OF TRIGEMINAL AUTONOMIC CEPHALGIAS

Feature	Cluster headache	Paroxysmal hemicrania	SUNCT and SUNA
Gender predominance	More common in males	Equal	About equal
Pain type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp
Pain site	Orbit, temple	Orbit, temple	Periorbital
Frequency of attacks	0.5–8/day	1–40/day (usually >5/day)	3–200/day
Duration of attacks	15–180 min	2–30 min	5–240 sec
Autonomic features	Yes	Yes	Yes (especially conjunctival injection and lacrimation)
Migrainous features	Yes	Yes	Yes, in about 1/3 of cases
Alcohol trigger	Yes	No	No
Cutaneous trigger	No	No	Yes
Indomethacin effect	No	Absolute response	No
Key abortive treatments	Sumatriptan (nasal,* subcutaneous), oxygen	Nil	Intravenous lignocaine*
Key preventive treatments	Verapamil,* methysergide, lithium,* corticosteroids (short term)*	Indomethacin*	Lamotrigine,* topiramate,* gabapentin*

Abbreviations: SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; SUNA = short-lasting unilateral neuralgiform headache with cranial autonomic symptoms.
* Off-label use.

the timing of attacks (typically 2200–0200, more common in the springtime), the duration of attacks (average 90 minutes *vs* 15 minutes), average number of daily attacks (one *vs* five) and their differential response to acute therapies.

Other potentially catastrophic causes of sudden headache should always be considered, particularly in acute presentations. These include aneurysmal disease, subarachnoid haemorrhage, arterial dissection and acute angle closure glaucoma (which may present with headache, tearing and redness of the eye, as well as agitation).

Pituitary gland pathology may accompany TACs – up to 10% of patients with pituitary tumours and headache present with a TAC phenotype.[4] MRI with pituitary views and pituitary function testing are thus appropriate in the workup of patients with an initial TAC presentation.

Cluster headache

Cluster headache affects around 0.1% of the population,[5] with a male predominance, a higher frequency in cigarette smokers, and peak onset in the second and third decade of life.[6] The headaches are severe and boring in quality, lasting 15 to 180 minutes, and typically occur in the orbital, supraorbital or temporal regions. Patients often describe the pain as the worst they have experienced, rivalling even childbirth. Marked agitation and restlessness are usually associated with cluster headache, in contrast with the avoidance of movement seen during attacks of migraine.[6] Patients are usually asymptomatic between attacks.

Cluster headaches tend to occur in bouts, with the attacks within a bout linked to the circadian rhythm, occurring at the same time each day. Also, bouts exhibit a circannual periodicity; they are often more frequent in spring or autumn, around the time that the clocks change for daylight saving, and typically last about eight to 10 weeks.

Alcohol, nitrates, exercise and warmth may trigger attacks, but only in 'at-risk' periods. The attacks may be associated with 'migrainous' features, such as photophobia, phonophobia, nausea and vomiting. However, the other clinical features and temporal pattern are so distinctive that diagnostic confusion between cluster headache and migraine should be rare.

Cluster headaches are classified according to the duration of the bout. Episodic forms occur in bouts lasting seven days to one year, with bouts separated by at least a one-month pain-free period, while a chronic cluster lasts for one year or longer, without remissions or with less than one month of remission.[7]

As headache resembling cluster headache may occur secondary to a number of structural pathologies, good quality imaging with MRI focused especially on the pituitary and cavernous sinus region is prudent in all cases.

Management of cluster headaches involves both preventive and acute treatment measures. Agents to abort the acute attack include:

- 100% oxygen administered at 12 to 15 L/min via a non-rebreather mask for 15 to 20 minutes
- subcutaneous sumatriptan 6 mg
- intranasal sumatriptan 20 mg

(off-label use, currently limited access in Australia).

Oral triptans are not usually helpful because by the time they become effective, the relatively short duration cluster headache is already spontaneously subsiding.

Preventive treatments are useful in patients with chronic cluster headache and may shorten the duration of the active period in those with the episodic form. Options for prevention depend on the length of the bout. Longer bouts require safe and effective agents that can be administered long term, such as verapamil, lithium and topiramate (all off-label uses), whereas shorter bouts may be managed by prednisolone (off-label use), which acts quickly but should not be used for long periods.

Verapamil often needs to be used at higher than usual doses, reached by gradually increasing the dose: up to 960 mg/day in split doses of the immediate release form has been used. There is a risk of conduction block occurring with higher doses, so two weekly monitoring with ECG after each dose increase to detect any emerging conduction block (lengthening of the PR interval) should be performed before the next increase. Six-monthly ECG can be performed when a stable dose is reached.[8]

A useful strategy for patients with episodic cluster headache is to use prednisolone (starting at 75 mg/day and weaning rapidly to zero over two to three weeks) as a means of gaining rapid control of the bout, and starting verapamil at low dose (for example, up to 80 mg thrice daily, increasing by up to 80 mg every two weeks) at the same time. The verapamil thus starts to have an impact as the prednisolone is weaned.

Other treatments include greater occipital nerve block (with corticosteroids and local anaesthetic) and surgical options for refractory cases (e.g. occipital nerve stimulators, posterior hypothalamic neurostimulation).[9,10]

SUNCT and SUNA

SUNCT and SUNA are rare TACs characterised by short-duration attacks of unilateral head pain with associated autonomic features, often triggered by cutaneous stimuli. SUNCT is defined by the presence of significant tearing and conjunctival injection, and SUNA by their absence; however, these conditions are clearly part of the same spectrum.

These headaches are an important differential diagnosis for trigeminal neuralgia. Key distinguishing features of SUNCT/SUNA include pain typically localised to the ophthalmic division of the trigeminal nerve (rare for trigeminal neuralgia) and the presence of autonomic features. Cutaneous triggers of pain paroxysms are often a feature of both trigeminal neuralgia and SUNCT/SUNA. However, trigeminal neuralgia is characteristically associated with a 'refractory period' during which the same cutaneous trigger is unable to reproduce the pain for a brief period after an attack.[11] The pain of SUNCT/SUNA may present as short-lived single stabs (lasting five to 240 seconds), groups of stabs, or a saw-tooth pattern where the pain does not return to baseline between stabs and the attack lasts several minutes.

Patients with these headaches show no response to indomethacin (see paroxysmal hemicrania) or to the typical relievers for cluster headache. The most effective treatment is lamotrigine, with some efficacy also seen for topiramate and gabapentin (all off-label uses). Ten days of intravenous lignocaine treatment may also induce a remission.[12]

Paroxysmal hemicrania

Paroxysmal hemicrania comprises short attacks of severe unilateral pain (lasting two to 30 minutes), typically in the ophthalmic division, occurring several times daily and accompanied by autonomic features. There is often associated unilateral photophobia and phonophobia, as well as restlessness and agitation. The attacks usually occur during the day, and a small percentage are triggered by alcohol or a manual trigger, such as head movement and pressure on C4 or C5, the C2 root or the greater occipital nerve. There are no cutaneous triggers, such as seen in SUNCT/SUNA. Paroxysmal hemicrania may be episodic (with remissions lasting more than one month) or chronic (with no remission in one year).

Paroxysmal hemicrania exhibits a lasting response to indomethacin; however, in patients intolerant to the gastric effects of this medication, the alternatives are less clearly defined. Cyclooxygenase-2 inhibitors, topiramate and greater occipital nerve block with lidocaine and methylprednisolone acetate may be beneficial (all off-label uses).[13]

Hemicrania continua

Hemicrania continua is a continuous side-locked headache of varying intensity. Exacerbations may be accompanied by ipsilateral autonomic symptoms as well as migrainous features (nausea, photophobia, phonophobia). The background pain in hemicrania continua is greater than the interparoxysmal pain seen in other TACs, and the exacerbations longer in duration – features that help distinguish it from paroxysmal hemicrania.

There is a complete resolution of the headache with therapeutic doses of indomethacin, which is one of the diagnostic criteria. Similarly to paroxysmal hemicrania, topiramate, greater occipital nerve block and occipital nerve stimulators have all been reported to be beneficial.[14,15]

An oral indomethacin test may be performed using a regimen of 25 mg thrice daily for one week, increasing to 50 mg thrice daily in the second week and 75 mg thrice daily in the third. The patient should keep a headache diary before and during the test so changes in pain scores can be evaluated. Prophylactic use of a proton pump inhibitor is advisable to reduce the risk of gastrointestinal complications. If the test is positive, the dose can be gradually decreased by 25 mg thrice daily every few weeks until the minimal effective dose is established.

Miscellaneous primary headaches

There are a number of other headache syndromes with characteristic patterns,

some of which occur after specific triggers. These conditions are not rare.

Primary stabbing headache

Primary stabbing headache, also known as 'jabs and jolts' or the more evocative 'ice-pick pains', is a term patients readily identify with, as the pain is often described as being like a very brief and localised stab into the head.

The pain occurs spontaneously (unprovoked), with 80% of stabs lasting three seconds or less. The attack frequency is generally low and will occur outside of the distribution of the trigeminal nerve in 70% of cases. Although the pain is often confined to one area, in some patients it may shift locations, including to the opposite side of the head. There are usually no accompanying symptoms such as nausea, photophobia or autonomic changes. Physical examination and imaging, if performed, are typically normal.

This condition is not rare, though many patients do not bother to report it. Others, however, may be concerned that it represents serious pathology and are reassured by a definite diagnosis. Rarely is the condition disabling, and most patients do not require treatment. Many patients with primary stabbing headache also experience migraine,[16] in which case the stabbing pains are felt predominantly on the side most affected during migraine attacks.

The differential diagnoses would include brief forms of TACs such as SUNCT and paroxysmal hemicrania, but these would typically have associated autonomic symptoms. A positive response to indomethacin in affected patients has been reported in some uncontrolled studies, whereas others have found partial or no response.

Cough headache

Cough headache is a headache of sudden onset, lasting from one second to 30 minutes, brought on by, and occurring only in association with, coughing, straining or the Valsalva manoeuvre.[17] It is typically bilateral, very abrupt in onset and reaches peak severity immediately. The pain then subsides gradually over 15 to 30 seconds, often with a pulsatile quality during this time.

In about 40% of cases, an underlying pathology is found. The most common such cause is Chiari malformation. This makes sense as the headache can be explained by failure of intracranial and intraspinal pressures to equilibrate immediately (as they normally do) after coughing or straining. The raised intrathoracic pressure is transmitted through the venous system to the intracranial cavity. If there is then a pressure gradient across the foramen magnum, pain will arise from traction on meninges, vessels and other pain-sensitive structures in the region. The pain wanes as pressures gradually equalise. Other reported causes include spontaneous intracranial hypotension, carotid or vertebrobasilar disease, and tumours in the middle or posterior fossa.

Cough headache obviously mandates careful imaging of the brain, and the region of the foramen magnum in particular. MRI provides excellent views of this area, but the radiologist must be alerted that this is the area of interest.

Patients with no abnormalities on imaging are classified as having 'primary cough headache', formerly called 'benign cough headache'. It is plausible that some cases may involve structural abnormalities too subtle to detect radiologically. The authors report one case in which the symptoms were relieved after surgical exploration of the region showed fine bands of arachnoid tissue that were then cleared away.

Cough headache often responds, at least partially, to indomethacin. However, this response occurs both in primary cases and in those with demonstrable obstruction, and is therefore not diagnostically specific.

Primary headache associated with sexual activity

Two subtypes of primary headache are associated with sexual activity ('benign sex headache'). The less common pre-orgasmic subtype starts as a dull bilateral ache in the head and neck that intensifies with sexual arousal and is often associated with awareness of neck or jaw muscle contraction. The more common and more severe form occurs at orgasm and is explosive and instantaneous in onset. It is thus a form of thunderclap headache and subarachnoid haemorrhage must be the provisional diagnosis until definitely excluded.

Orgasmic headache is severe and patients are typically appropriately anxious about a serious cause; once this is excluded, they remain anxious about the effect recurrent headaches might have on their quality of life. The natural history of orgasmic headache is for recurrences to occur (with sexual activity or with lifting or straining) over a period of a few weeks and then for the condition to subside. During the period of susceptibility, indomethacin may provide some symptomatic relief and there is some anecdotal evidence that beta blockers (such as propranolol) or calcium channel blockers (such as verapamil) may also be of value (all off-label uses).

There are many similarities between orgasmic headache and the thunderclap headache seen in reversible cerebral vasoconstriction syndrome (RCVS). RCVS may cause single or recurrent episodes (over a few weeks) of instantaneous headache and is diagnosed when computed tomography angiography, magnetic resonance angiography or other vascular imaging shows vasospasm. It may be triggered by various stimuli, often of an adrenergic nature (such as cocaine or amphetamine use), but also by sexual activity.

It is tempting, therefore, to conclude that many cases of orgasmic headache may be a version of RCVS. In a recent study in which detailed vascular imaging was carried out in 30 patients with orgasmic headache, 60% had evidence of RCVS.[18] Importantly, clinical features were similar in those with and without vasospasm on imaging, suggesting considerable overlap between the two conditions.

Primary exercise headache

Primary exercise headache, previously called primary or benign exertional headache, likely represents a heterogenous group of conditions. Its pathophysiology

is unknown, but it is believed to have a vascular origin, with researchers hypothesising that venous or arterial distension secondary to exercise is the pain-inducing mechanism. It typically occurs after intense physical activity, particularly in hot weather or at high altitude, with 'weightlifter's headache' being a recognised subtype.

Exercise headache is not uncommon. One survey found 30% of adolescents experienced headaches during or after physical activity. These headaches were often bilateral, pulsating and brief (lasting less than an hour).[19] Migraine was a predisposing factor: 47% of individuals with migraine reported exercise headache, compared with 21% of those without.

Hypnic headache

Hypnic headache is a rare primary headache disorder, predominantly affecting older adults (average age of onset is about 60 years). It is characterised by headaches that occur exclusively during sleep, typically once or twice nightly, and are disruptive enough to wake the patient.[20] The pain may be unilateral or bilateral and is usually severe or at least moderately severe.

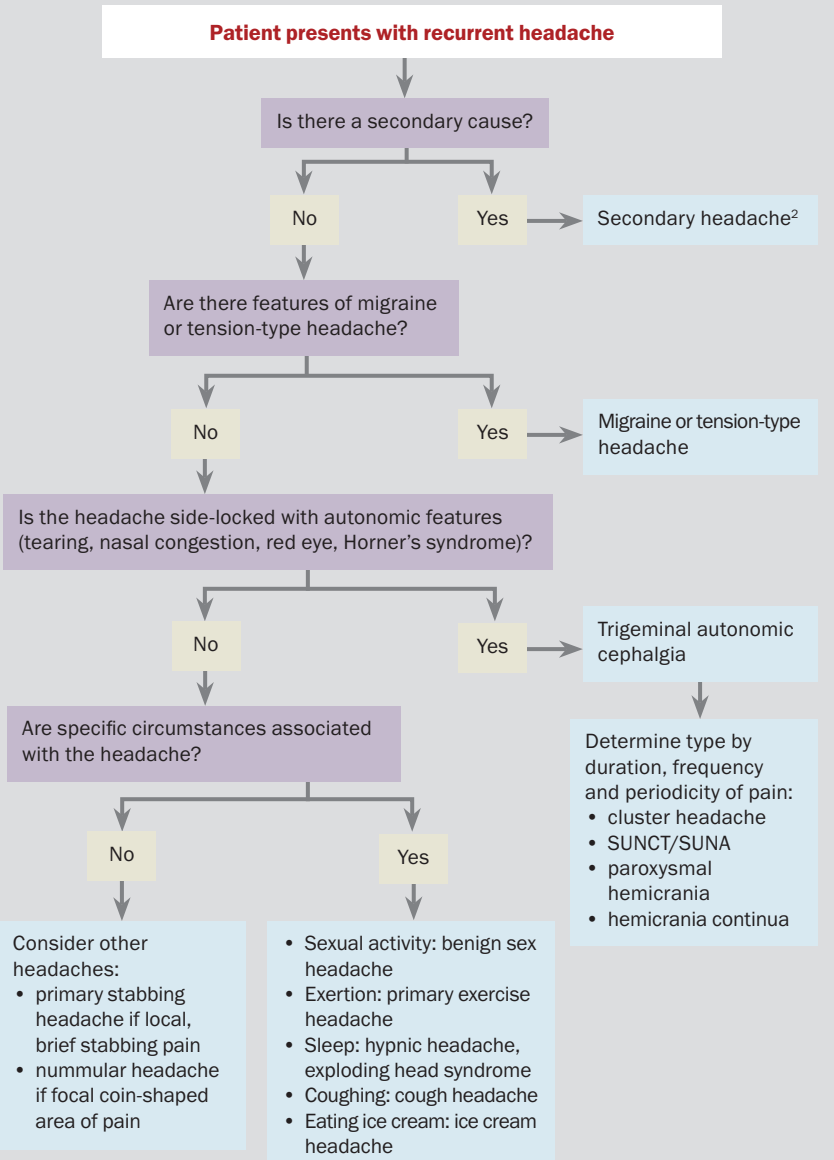
Patients often find some relief by getting up and moving about, and many report that drinking caffeine helps. Prophylactic treatments that are sometimes effective include caffeine before bed, lithium, topiramate, indomethacin, melatonin and amitriptyline (all off-label uses).

Nummular headache

Nummular headache is a rare primary headache disorder in which there is a focal 'coin-shaped' circumscribed area of pain, two to six cm in diameter (from the Latin *nummulus*, a small coin).[21] Nummular headache is typically persistent in type with some superimposed exacerbations of more severe pain (which is still usually described as a dull ache). Sharp pain or local tenderness is rare.

No treatment is reliably effective, although there is an anecdotal report of benefit from botulinum toxin injection in a small number of patients.[22] The natural history is very variable: some cases resolve spontaneously, whereas others may persist for years.

DIAGNOSTIC APPROACH TO UNUSUAL PRIMARY HEADACHES



Abbreviations: SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; SUNA = short-lasting unilateral neuralgiform headache with cranial autonomic symptoms.

Exploding head syndrome

Exploding head syndrome involves alarming but painless episodes described as a loud 'explosion' in the head. Attacks tend to occur at the onset of sleep, even at the start of daytime naps.

This condition is probably not rare. When Pearce first described 10 cases with this evocative name, it received substantial press coverage, and he was then inundated with correspondence describing similar cases. Within a year, he was able to publish

a review of 50 well-documented cases.[23] The cause remains uncertain but the timing suggests a similarity to the other physiological phenomena, such as nocturnal myoclonus, that mark the transition from wakefulness to stage one sleep.

No established treatment exists, but clomipramine has been used anecdotally.

Ice cream headache

Ice cream headache is so common that it is almost a normal phenomenon. It is termed officially (but more prosaically) as 'headache attributed to ingestion or inhalation of a cold stimulus'. The short-lasting pain, which may be severe, is induced in susceptible individuals by the passage of cold material over the palate or posterior pharyngeal wall.

Ice cream headache affects about 40% of adolescents.[24] Like exercise headache, it occurs more often in individuals with migraine: one study reported it in 55% of people with migraine, compared with 29% of those with no background history of headache.[24] Another study found that cold-induced headache was triggered experimentally in 74% of people with migraine (who often reported unilateral throbbing pain) and in only 32% of patients with tension-type headache (whose pain was usually bilateral and not throbbing).[25]

Summary

Although some of the primary headache disorders are relatively uncommon, GPs will occasionally encounter them in practice. The strictly unilateral nature and associated autonomic features of the TACs are strong diagnostic clues. For many of the other headache types, specific trigger factors (sexual activity, exertion, sleep or coughing) can offer diagnostic clues. The flowchart provides a diagnostic approach to patients presenting with recurrent headaches. MT

References

1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd ed. Cephalalgia 2018; 38(Suppl 1): 1-211.
2. Stark RJ. Headache: Investigating the cause. Med Today 2025; 26(7 Suppl): 2-7.
3. Irimia P, Cittadini E, Paemeleire K, Cohen AS, Goadsby PJ. Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. Cephalalgia 2008; 28: 626-630.
4. Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. Brain 2005; 128: 1921-1930.
5. Tonon C, Guttmann S, Volpini M, Naccarato S, Cortelli P, D'Alessandro R. Prevalence and incidence of cluster headache in the Republic of San Marino. Neurology 2002 14; 58: 1407-1409.
6. Lambru G, Matharu MS. Trigeminal autonomic cephalalgias: a review of recent diagnostic, therapeutic and pathophysiological developments. Ann Indian Acad Neurol 2012; 15(Suppl 1): S51-S61.
7. Matharu MS, Goadsby PJ. Trigeminal autonomic cephalgias. J Neurol Neurosurg Psychiatry 2002; 72(Suppl 2): ii19-ii26.
8. Cohen AS, Matharu MS, Goadsby PJ. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. Neurology 2007; 69: 668-675.
9. Burns B, Watkins L, Goadsby PJ. Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. Neurology 2009; 72: 341-345.
10. Leone M, Proietti Cecchini A, Franzini A, et al. Lessons from 8 years' experience of hypothalamic stimulation in cluster headache. Cephalalgia 2008; 28: 787-797; discussion 798.
11. Cohen AS, Matharu MS, Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA) – a prospective clinical study of SUNCT and SUNA. Brain 2006; 129: 2746-2760.
12. Matharu MS, Cohen AS, Boes CJ, Goadsby PJ. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing syndrome: a review. Curr Pain Headache Rep 2003; 7: 308-318.
13. Cohen AS, Goadsby PJ. Paroxysmal hemicrania responding to topiramate. J Neurol Neurosurg Psychiatry 2007; 78: 96-97.
14. Brighina F, Palermo A, Cosentino G, Fierro B. Prophylaxis of hemicrania continua: two new cases effectively treated with topiramate. Headache 2007; 47: 441-443.
15. Burns B, Watkins L, Goadsby PJ. Treatment of hemicrania continua by occipital nerve stimulation with a bion device: long-term follow-up of a crossover study. Lancet Neurol 2008; 7: 1001-1012.
16. Guerrero AL, Herrero S, Peñas ML, et al. Incidence and influence on referral of primary stabbing headache in an outpatient headache clinic. J Headache Pain 2011; 12: 311-313.
17. Calandre L, Hernandez-Lain A, Lopez-Valdes E. Benign Valsalva's maneuver-related headache: an MRI study of six cases. Headache 1996; 36: 251-253.
18. Yeh YC, Fuh JL, Chen SP, Wang SJ. Clinical features, imaging findings and outcomes of headache associated with sexual activity. Cephalalgia 2010; 30: 1329-1335.
19. Chen SP, Fuh JL, Lu SR, Wang SJ. Exertional headache – a survey of 1963 adolescents. Cephalalgia 2009; 29: 401-407.
20. Holle D, Naegel S, Krebs S, et al. Clinical characteristics and therapeutic options in hypnic headache. Cephalalgia 2010; 30: 1435-1442.
21. Moon J, Ahmed K, Garza I. Case series of sixteen patients with nummular headache. Cephalalgia 2010; 30: 1527-1530.
22. Mathew NT, Kailasam J, Meadors L. Botulinum toxin type A for the treatment of nummular headache: four case studies. Headache 2008; 48: 442-447.
23. Pearce JM. Clinical features of the exploding head syndrome. J Neurol Neurosurg Psychiatry 1989; 52: 907-910.
24. Fuh JL, Wang SJ, Lu SR, Juang KD. Ice-cream headache – a large survey of 8359 adolescents. Cephalalgia 2003; 23: 977-981.
25. Selekler HM, Erdogan MS, Budak F. Prevalence and clinical characteristics of an experimental model of 'ice-cream headache' in migraine and episodic tension-type headache patients. Cephalalgia 2004; 24: 293-297.

COMPETING INTERESTS: Dr Hutton has served on advisory boards for Sanofi-genzyme, Novartis, Teva, Eli Lilly, Allergan and Lundbeck; been involved in clinical trials sponsored by Novartis, Teva, Xalud and Cerecin; and received payment for educational presentations from Allergan, Teva, Eli Lilly and Novartis. Dr Ray has received honoraria for educational presentations for AbbVie, Novartis and Viatris. He has served on medical advisory boards for Pfizer, Viatris and Eli Lilly. His institution has received funding for research grants, clinical trials and projects supported by the International Headache Society, Brain Foundation, Lundbeck, AbbVie, Pfizer and Aeon. Professor Stark has served on advisory boards for Teva, Eli Lilly, AbbVie, Viatris and Lundbeck; and received payment for educational presentations from AbbVie, Teva, Eli Lilly and Viatris.

Thunderclap headache

When the risk of doing nothing is too high

SHULI CHENG MB BS, FRACP
RICHARD J. STARK AM, MB BS, FRACP, MACLM

A thunderclap headache is an uncommon presentation of headache but is important to recognise because it is often associated with serious vascular intracranial disorders, and should therefore be investigated urgently. Aneurysmal subarachnoid haemorrhage is the foremost consideration, and reversible cerebral vasoconstriction the next most common cause. The causes and diagnostic approach to patients with thunderclap headache are discussed.

Thunderclap headache is often associated with serious vascular intracranial disorders, particularly subarachnoid haemorrhage (SAH). The search for an underlying cause should be immediate and exhaustive. This article discusses the causes and diagnostic approach to patients with thunderclap headache.

Definitions and clinical presentation

Thunderclap headache is a high-intensity headache of abrupt onset, generally reaching maximum intensity in less than one minute and lasting for five minutes or longer, according to

MedicineToday 2025; 26(7 Suppl): 33-37
First published in Medicine Today 2017; 18(7): 14-19
Updated July 2025

Dr Cheng is a Neurologist in the Neurology Department, The Alfred Hospital, Melbourne. Professor Stark is a Neurologist in the Neurology Department, The Alfred Hospital, Melbourne; and Adjunct Clinical Professor in the Department of Neuroscience, Monash University, Melbourne, Vic.

KEY POINTS

- **The cause of thunderclap headache should be considered to be aneurysmal subarachnoid haemorrhage until proven otherwise.**
- **The diagnostic workup involves urgent nonenhanced CT of the brain (with CT angiography if immediately available), then possibly a lumbar puncture, and then cerebral arterial and venous imaging with either MRI or CT if each preceding investigation has yielded a normal or negative result.**
- **Reversible cerebral vasoconstriction syndrome is usually characterised by recurrent thunderclap headaches and multifocal, multivessel segmental cerebral artery vasoconstriction that usually resolve within 12 weeks. It can be associated with neurological complications including intracerebral haemorrhage and cerebral ischaemic infarctions.**

1. FEATURES SUGGESTIVE OF SUBARACHNOID HAEMORRHAGE

Key feature

- Thunderclap headache

Possible associated features

- Focal neurological symptoms or signs such as focal weakness or sensory change
- Altered consciousness
- Meningismus
- Collapse
- Vomiting at onset

The International Classification of Headache Disorders, 3rd edition.[1] A practical diagnostic aid is to snap one's fingers at the patient and ask: 'Did it come on like this?' The description 'most severe ever headache' does not, by itself, establish the diagnosis of thunderclap headache.

The history alone is often insufficient to determine the cause of the thunderclap headache with certainty. It is necessary to enquire about a prior history of headaches, recurrence of the thunderclap headache, the events around the onset of the headaches (sexual activity, physical activity, bath, cough, Valsalva manoeuvre), head and neck trauma, drugs used (serotonergic and sympathomimetic medications and illicit drugs) and pregnancy and postpartum status.

Certain symptoms and signs are more suggestive of certain underlying causes; for example, focal neurological symptoms or signs, altered consciousness, meningism, collapse or vomiting at onset would raise suspicion of a subarachnoid or even intracerebral haemorrhage (Box 1).

Causes

The list of causes of thunderclap headache is extensive, with the rare causes frequently reported in the medical literature as case reports only.[2] The list can be divided into the following groups to assist with clinical reasoning (Box 2):

- aneurysmal SAH
- cerebrovascular disease with evidence of vasoconstriction – particularly reversible cerebral vasoconstriction syndrome (RCVS)
- cerebrovascular disease with no evidence of segmental arterial constriction, i.e. nonvasoconstrictive aetiology – includes intracranial haemorrhage (subdural, subarachnoid, intraparenchymal, epidural), ischaemic stroke, arterial dissection, cerebral venous sinus thrombosis, inflammatory arteriopathy and hypertensive encephalopathy
- infections – includes viral illness, rhinosinusitis, aseptic and bacterial meningitis
- nonvascular neurological causes – includes intracranial hypotension, pituitary apoplexy, cerebral neoplasms and colloid cyst of the third ventricle
- primary headache triggered by provoking factors – includes primary cough headache, bath-related thunderclap headache, primary exercise headache and primary headache associated with sexual activity
- systemic illness – includes acute myocardial infarction, aortic dissection and phaeochromocytoma.

Diagnostic workup

Following the history and physical examination, all patients with thunderclap headache should be managed as a medical emergency to avoid potentially catastrophic consequences from SAH and other intracranial causes of the headache. SAH is usually detected by brain CT imaging and the site of bleeding is often apparent on CT angiography (Figure 1 and Figure 2).

If a patient presents two weeks or more after thunderclap headache, the top priority is to exclude an underlying aneurysm or other structural cause rather than to try to demonstrate subarachnoid blood. Proceeding directly to brain CT with CT angiography or MRI with magnetic resonance angiography would be appropriate.

The flowchart shows an approach to the diagnostic workup of a patient with thunderclap headache.

2. CAUSES OF THUNDERCLAP HEADACHE[2]

- Aneurysmal subarachnoid haemorrhage (in about 25% of patients with thunderclap headache)
- Cerebrovascular disease with evidence of vasoconstriction (particularly reversible cerebral vasoconstriction syndrome)
- Cerebrovascular disease of nonvasoconstrictive aetiology
- Infections
- Nonvascular neurological causes
- Primary headache triggered by provoking factors
- Systemic illness

Brain CT scanning and angiography

The first investigation should be a brain CT scan to evaluate for SAH and other intracranial causes of thunderclap headache (Figure 1). If available immediately, CT angiography of the head should be performed at this time also (Figure 2).

The brain CT scan should be performed as soon as possible after the onset of the headache. CT brain imaging performed in the first six to 12 hours has a specificity of 98% and a sensitivity of close to 100% for detecting SAH. However, the sensitivity of CT to detect a SAH progressively declines as the interval between the headache and the CT imaging lengthens: it is about 85% to 95% on day two, about 75% on day three and about 50% after day five.[3] The sensitivity is reduced in small volume bleeds, if the CT scan is not reviewed by an experienced reviewer or if the symptoms are atypical.

Lumbar puncture

A lumbar puncture is indicated if a brain CT scan or CT angiography does not reveal the aetiology of the thunderclap headache.

The classic findings of SAH on lumbar puncture are an elevated opening pressure and an elevated red blood cell count that

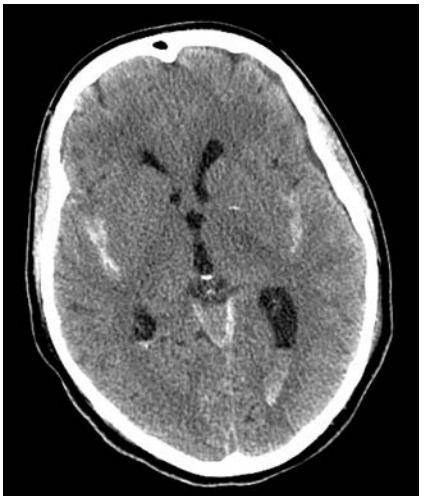


Figure 1. CT scan showing subarachnoid blood in the sylvian fissures and lateral ventricle.
Courtesy of Dr Anthony Kam, Melbourne, Vic.

does not diminish from cerebrospinal fluid tube one to tube four, and the presence of xanthochromia.

Xanthochromia represents haemoglobin degradation products. This indicates that blood has been in the cerebrospinal fluid for at least two hours. Xanthochromia is detected visually by comparing a vial of cerebrospinal fluid with a vial of plain water held side by side against a white background in bright light or by formal spectrophotometric analysis. Spectrophotometry detects bilirubin and is highly sensitive when the lumbar puncture is performed at least 12 hours after the SAH. Xanthochromia can last for two weeks or more.[4]

Further analysis of the cerebrospinal fluid includes cell counts and measurement of protein and glucose levels, and microscopy and culture to test for infections in the central nervous system.

MRI and angiography

Patients who have nondiagnostic brain CT scans and lumbar puncture results should be further evaluated with contrast-enhanced brain MRI and noninvasive vascular imaging of the head and neck (magnetic resonance angiography or CT angiography). This imaging can detect arterial dissections and vasoconstriction syndromes.

CT venography and magnetic resonance venography

Venous sinus imaging via CT or magnetic resonance venography is indicated if clinical suspicion for a cerebral venous thrombosis is high.

Subarachnoid haemorrhage

About 70% of patients with SAH present with headaches as the main symptom, and about 50% of these present with thunderclap headache. SAH is found in up to 25% of patients with thunderclap headache. Aneurysmal SAH is therefore the diagnosis of foremost consideration in this scenario.

The brain CT scan and/or the lumbar puncture would be expected to yield a positive result in patients with SAH. Magnetic resonance angiography or CT angiography will often detect aneurysms, but only those larger than 3 mm. Formal four-vessel catheter angiography (digital subtraction catheter angiography) is the gold standard to determine the site and morphology of the aneurysm and to guide treatment (angiography with a catheter also offers the possibility of coiling the aneurysm).

Treatment of SAH is highly specialised and patients require management in a well-equipped expert neurosurgical unit. Management includes supportive care and avoidance of vasoconstriction, which may produce cerebral ischaemia. The cornerstone of treatment is to prevent further bleeding from the cause (usually an aneurysm). This requires surgical securing of the aneurysm (by clipping) or endovascular treatment (with coils and similar devices).

Reversible cerebral vasoconstriction syndrome

A greater understanding of RCVS has emerged in the past few years because of the wider availability of relatively noninvasive technologies to assess the cerebral vasculature. This syndrome has been given various labels (e.g. Call–Fleming syndrome, benign angiopathy of the central nervous system, postpartum angiopathy and

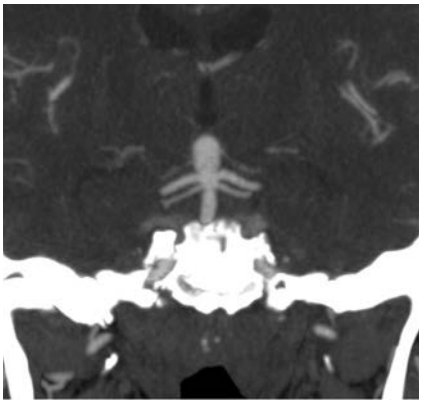


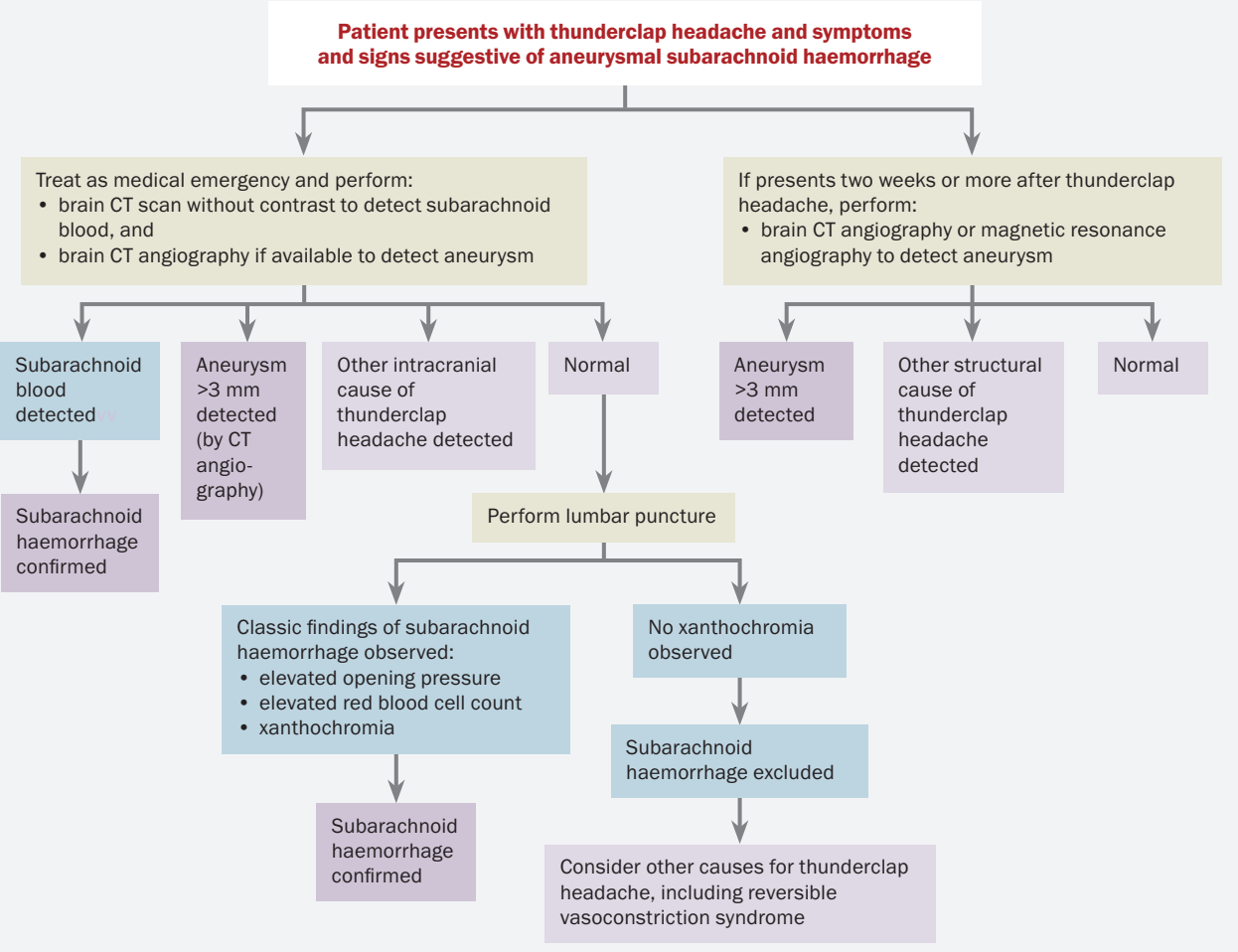
Figure 2. CT angiogram showing aneurysm at the tip of the basilar artery.
Courtesy of Dr Anthony Kam, Melbourne, Vic.

migrainous vasospasm), and can occasionally be confused with cerebral vasculitis because of overlapping angiographic and clinical features. The term 'reversible' refers to the intracranial artery vasoconstriction and not the possible permanent neurological deficits secondary to complications including intracerebral haemorrhage and cerebral ischaemic infarctions. RCVS may occur at any age, but many patients are young. Although most patients recover fully, a minority suffer permanent cerebral ischaemic damage.

The diagnostic criteria for RCVS include (Box 3):[5]

- thunderclap headache(s) with or without focal neurological deficits or seizures
- often recurrent episodes of thunderclap headache during the first month but usually no new symptoms appearing after this time
- multifocal, multivessel, segmental vasoconstriction of cerebral arteries. The vessels involved may be main trunks of vessels such as middle or posterior cerebral arteries but are often more peripheral branches. The changes may be obvious but are sometimes subtle and only detected when the radiologist is alerted to this as a possible diagnosis (Figure 3)
- absence of aneurysmal SAH
- normal or near normal

AN APPROACH TO THE DIAGNOSTIC WORKUP FOR ANEURYSMAL SUBARACHNOID HAEMORRHAGE AS A CAUSE OF THUNDERCLAP HEADACHE



cerebrospinal fluid analysis
- complete or substantial normalisation of cerebral arteries within 12 weeks of symptom onset.

RCVS can occur without an identifiable precipitating factor, during pregnancy or the puerperium period and as an idiosyncratic response to certain medications (selective serotonin reuptake inhibitors and nasal decongestants have been implicated) or illicit drugs (either acute or chronic use) and in the setting of catecholamine-secreting tumours. It can be provoked by sexual activity, exertion or Valsalva manoeuvres, emotions and bathing or showering.

It is usual to have multiple thunderclap headaches over one to four weeks, sometimes with a baseline lingering headache in between. A small percentage of patients (5%) have recurrences after this period.

Lumbar puncture analysis is typically normal in patients with RCVS. A significantly abnormal cerebrospinal fluid analysis (with pleocytosis) should prompt consideration of the differential diagnosis of primary angiitis of the central nervous system, a rare condition, or other forms of cerebral vasculitis. Radiologists often raise the question of cerebral vasculitis in RCVS cases but RCVS is much more common than cerebral vasculitis, especially when the presentation is thunderclap headache.

Brain CT and MRI scans are normal in uncomplicated RCVS but can reveal abnormalities otherwise. Early complications, mainly occurring in the first week of symptoms, include cortical SAH (usually very localised within a sulcus as opposed to the widespread SAH typically seen after ruptured aneurysm), intracerebral haemorrhage and cerebral vasogenic oedema, as seen in the posterior reversible encephalopathy syndrome. Ischaemic events, including transient ischaemic attacks and cerebral infarction, occur mainly in the second week. In one study, these complications occurred at rates of cortical SAH, 22%; intracerebral haemorrhage, 6%; cerebral vasogenic

3. DIAGNOSTIC CRITERIA FOR REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROMES[4]

- Thunderclap headache(s) with or without focal neurological deficits or seizures; often recurrent in first month
- Usually no new symptoms after the first month
- Vasoconstriction of cerebral arteries – multifocal, multivessel, segmental
- Absence of aneurysmal SAH
- Normal or near normal CSF analysis
- Normalisation (near or complete) of cerebral arteries within 12 weeks of symptom onset

Abbreviations: CSF = cerebrospinal fluid; SAH = subarachnoid haemorrhage.

oedema, 9%; transient ischaemic attacks, 16%; and cerebral infarction, 4%.[6]

Angiography (magnetic resonance or CT) in RCVS will reveal multifocal vasoconstriction of multiple intracranial arteries that is maximal at about two to three weeks after symptom onset. The pattern is one of distal vasoconstriction initially, which may then move more proximally in the first several weeks after symptom onset, and then resolves (is 'reversible'). Normal vasculature on initial angiography should prompt repeat vascular imaging in a few weeks to search for vasoconstriction.

Treatment for RCVS is still guided by observational and anecdotal experience. Identifying the precipitating factors or disease guides treatment (e.g. discontinuation of vasoactive drugs, resection of catecholamine-secreting tumours). There is probably a role for the off-label use of calcium channel blockers (nimodipine or verapamil) as first-line treatment. Short-term use of high-dose glucocorticoids is controversial: it had been reported as effective based on reversal of vasoconstriction in experiments but has been accused of worsening clinical outcomes.[7] Some argue that simple observation with follow-up imaging may be reasonable as the disease course is self-limiting.[5] Avoiding further vasoconstrictors, such as ergots and triptans, would seem prudent.

Primary headaches

Although there are diagnostic criteria in *The International Classification of Headache Disorders*, 3rd edition, for primary thunderclap headache, the evidence that this exists as a primary disorder is poor and this diagnosis should only be made with caution and as a last resort.[1]

Other primary headaches that are provoked (i.e. primary cough headache, primary exercise headache and primary headache associated with sexual activity) have a number of possible secondary causes as well, which must first be ruled out.

There is now increasing evidence that primary thunderclap headache, some of the primary headaches that are provoked and RCVS are part of the same spectrum. For example, many cases of headache associated with sexual activity (so-called 'benign sex headache') were shown on careful angiography (CT or magnetic resonance) to have cerebral vasoconstriction as expected in RCVS; these cases were clinically indistinguishable from those in whom cerebral vasoconstriction was not found.[8] Furthermore, these conditions often follow a similar time course, and patients with headache associated with sexual activity will be at risk of recurrent episodes for four to six weeks but may then never experience them again, just like those with proven RCVS.

Conclusion

A thunderclap headache is an uncommon presentation of headache but is important to recognise because it should prompt urgent medical review and investigation as it is often associated with serious vascular intracranial disorders. Aneurysmal SAH is the foremost consideration. Understanding of RCVS is expanding and this is probably the next most common cause for thunderclap headache. The clinical importance of these disorders highlights the need for a precise history of how a headache develops and evolves. Any instantaneous onset headache requires urgent and careful evaluation. MT

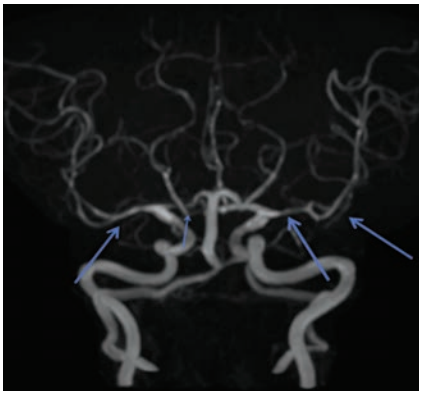


Figure 3. Magnetic resonance image showing irregularity of the middle cerebral artery branches bilaterally (arrows) in reversible cerebral vasoconstriction syndrome. Note the segmental vasoconstriction in several vessels.
Courtesy of Dr Joseph Nogajski, Sydney, NSW.

References

1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalagia 2018; 38: 1-211.
2. Devenney E, Neale H, Forbes RB. A systematic review of causes of sudden and severe headache (thunderclap headache): should lists be evidence based? J Headache Pain 2014; 15: 49.
3. Beckes D, Rinkel G, Kemperman H, Linn FH, Vergouwen MD. Time-dependent test characteristics of head computed tomography in patients suspected of nontraumatic subarachnoid haemorrhage. Stroke 2012; 43: 2115-2119.
4. Vermeulen M, Hasan D, Blijenberg BG, Hijdra A, Van Gijn J. Xanthochromia after subarachnoid haemorrhage needs no revisitation. J Neurol Neurosurg Psychiatry 1989; 52: 826-828.
5. Calabrese L, Dodick D, Schwedt T, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med 2007; 146: 34-44.
6. Ducros A, Boulkobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain 2007; 130: 3091-3101.
7. Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. Arch Neurol 2011; 68: 1005-1012.
8. Yeh Y, Fuh JSC, Wang SJ. Clinical features, imaging findings and outcomes of headache associated with sexual activity. Cephalalgia 2010; 30: 1329-1335.

COMPETING INTERESTS: Dr Cheng: None. Professor Stark has served on advisory boards for Teva, Eli Lilly, AbbVie, Viatris and Lundbeck; and received payment for educational presentations from AbbVie, Teva, Eli Lilly and Viatris.

Medication overuse headache

Less is MOH

LAKSHINI GUNASEKERA BBMed, MD, FRACP
JASON C. RAY MB BS, FRACP, PhD
RICHARD J. STARK AM, MB BS, FRACP, MACLM

Patients with headaches often self-treat their pain with analgesics. Overusing any pain medications can lead to more frequent headaches, which in turn causes a separate headache disorder termed medication overuse headache (MOH). GPs are in a prime position to identify MOH and prevent the condition from occurring through patient education and use of appropriate preventive therapy.

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Key points

- **An estimated 3 million people live with migraines in Australia, with at least a quarter of them having medication overuse headache (MOH).**
- **MOH occurs when a patient with a pre-existing headache disorder has a headache on 15 or more days of the month, for at least three months, because of overuse of symptomatic headache medications.**
- **Any analgesic can contribute to MOH and lead to more frequent, disabling headaches that are more difficult to treat.**
- **Education, reduction in analgesic use and commencement of effective preventive treatment can improve headache frequency.**

Medication overuse headache (MOH) is a type of secondary headache disorder in which the excessive use of pain medications (usually to treat primary headache disorders) can lead to further headaches.[1] MOH has a worldwide prevalence of 1 to 3% in the general population.[2,3] In Australia, it is estimated that there are 3 million people living with migraines and at least a quarter of them have MOH.[4] MOH has also been known as drug-induced headache, medication misuse headache and rebound headache.[1] MOH occurs when a patient with a pre-existing headache disorder has a headache on 15 or more days of the month, for at least three months, because of overuse of symptomatic headache medications.[1]

Patients who have headaches often self-treat their pain before seeking medical attention. If this strategy fails at home, they usually present to their GP requesting more pain medication or 'stronger' pain medication. GPs are thus in a prime position to identify MOH and prevent the condition from occurring through patient education and use of appropriate preventive therapy. Unfortunately, if this serious condition is not recognised, it can lead to escalating analgesic use, which in turn causes more frequent headaches that are more disabling and less responsive to many preventive treatments.

This article aims to increase awareness about the common entity of MOH, its causes and the key steps in its management. Importantly, we hope to convey that:

- although some analgesics are worse than others, any analgesic can contribute to MOH
- MOH is a maladaptive process in the brain, it is not just a 'rebound' headache
- MOH is a separate issue to addiction.

MedicineToday 2025; 26(7 Suppl): 38-40
First published in Pain Management Today 2024; 11(1): 66-69

Dr Gunasekera is a Neurologist and Headache Fellow in the Department of Neurology, Alfred Health, Melbourne; and PhD candidate in the Department of Neurosciences, Monash University, Melbourne. Dr Ray is a Neurologist in the Department of Neurology, Alfred Health, Melbourne and in the Department of Neurology, Austin Health, Melbourne; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne. Professor Stark is a Neurologist in the Neurology Department, The Alfred Hospital, Melbourne; and Adjunct Clinical Professor in the Department of Neuroscience, Monash University, Melbourne, Vic.

What is MOH?

MOH develops in a patient with a pre-existing headache disorder, which can be any of migraine, tension-type headache, chronic cluster headache, new daily persistent headache and possibly secondary headache disorders.[2] MOH is not thought to occur in patients without headaches who overuse pain medications.[2] Furthermore, patients with pre-existing headache disorders may not realise that the use of pain medications for non-headache reasons, such as joint pain, can also contribute to MOH.

MOH should be considered in patients who have 15 or more headache days per month and are overusing acute analgesia. The definition of 'medication overuse' depends on the medication used (Table 1).[1] There is still a lot we do not know about MOH. For example, we do not know how the cumulative daily dose of a medication impacts the risk of MOH.

MOH is a clinical diagnosis, with no specific history findings, examination findings, blood test results or scan results guiding the diagnosis.[4] This is why the medication history is crucial. Patients suspected of having this condition find it beneficial to keep a pain medication diary to quantify how much of each medication is being taken on a monthly basis.

The pathophysiology of MOH is multifactorial. There is evidence that chronic exposure to pain medications can lead to:

- downregulation of the receptors and enzymes they work on, thereby requiring higher doses of analgesics to achieve the same analgesic effect[5]
- central sensitisation, whereby pain signals are amplified with a corresponding reduced pain threshold – both of which would exacerbate the headache[2]
- modulation of gene and protein expression involved in migraine pathogenesis[2]
- suppression of brainstem modulatory systems and increase in cortical hyperexcitability, lowering the threshold to induce pain and altering the perception of pain.[2]

Management of MOH

Prevention is the best treatment for MOH. Every patient with a primary headache disorder should:

- be counselled on the safe monthly limits of analgesics, in the same way they are counselled on safe daily limits
- be considered for preventive treatment if they have more than four attacks per month or disabling or difficult to treat attacks. This will give them the confidence to be able to to take their analgesic when needed
- have their acute treatment plan optimised, as effective early treatment limits the need for multiple days of medication use.

If a patient is diagnosed with MOH, there are several steps involved in managing the condition. It is important not to blame patients for excessive medication use and it can be helpful to educate patients that the disease is distinct from addiction, which can carry significant stigma. As patients are generally overusing medications out of necessity to manage unbearable pain, an empathetic approach can go a long way. It is important to strike a balance between the under-treatment of pain (which can occur if we deprescribe) and the overuse of medications for headaches, which can lead to worsening of pain.

There are five main steps in the management of MOH, which incorporate short- and longer-term goals for the patient. These five steps are:

- patient education
- safe cessation of offending medication(s)
- management of acute symptoms
- consideration of an appropriate preventive agent
- consideration of when to refer to a specialist or multidisciplinary chronic pain service.

Patient education

Education about the entity of MOH is crucial because many patients may not know that their pain medication has the potential to cause pain if it is taken inappropriately. Patients may find it hard to understand why their pain medication needs to be stopped for their pain to improve. Some patients may struggle to stop using the pain medication as they believe it to be 'the only thing that helps with the pain'. As the treatment approach may seem counterintuitive, adequate education is crucial to increase adherence with the treatment plan and to prevent relapse. Repetition of the information across multiple clinic reviews can be useful for knowledge retention.

Safe cessation of offending medication(s)

Withdrawal of the causative medication of MOH or significant reductions in its use will help patients with MOH. Medications such as triptans, paracetamol and NSAIDs may be abruptly stopped without a weaning period.[5] Opioids may require a dose reduction before withdrawal, depending on the type and dose.[6] Patients should be counselled that if they are stopping analgesic use abruptly, they can expect a transient worsening of their headaches, and this can be managed. In the much longer term, once MOH is 'cured', appropriate analgesics can be reintroduced, ensuring that they heed the safe usage recommendations presented in Table 1.

Management of acute symptoms

Patients may develop a worsening of their headaches on withdrawal of pain medications. In the experience of the authors, this can last up to two to three weeks, depending on the medication. In the community setting, there are several strategies that can help patients manage this transition (Table 2). In principle, if a patient is already overusing a particular class of therapy, it cannot be used as an effective bridging therapy (for example, you cannot bridge naproxen in the setting of ibuprofen overuse). Nonpharmacological therapy can also be useful to help patients through the worst of the pain once the offending agents have been deprescribed. For example, ice packs, heat packs, massage and meditation can be used to alleviate pain, either as an adjunct to bridging therapy or as an alternative to pharmacological therapy.

For some patients, their symptoms are too severe to allow successful withdraw of the offending medication. More advanced strategies

Table 1. Medications with potential to cause medication overuse headache (MOH) and their threshold for use

Medication class	Examples	Threshold for MOH
Triptans	Sumatriptan, rizatriptan, eletriptan, naratriptan, zolmitriptan	• Risk of MOH if ≥10 days of use per month • Aim to use a maximum of two times per week
Paracetamol		• Risk of MOH if ≥15 days of use per month
NSAIDs	Aspirin, celecoxib, diclofenac, ibuprofen, indomethacin, meloxicam	• Risk of MOH if ≥15 days of use per month
Opioids	Codeine, oxycodone, tramadol	• There is no safe use of opioids for primary headache disorders – avoid if possible • If used as a last resort, limit to <10 days per month
Combination analgesics	Paracetamol/ codeine	• Risk of MOH if ≥10 days of use per month

include greater occipital nerve blocks by an appropriately trained clinician or hospitalisation and consideration of inpatient infusion.[7] For most patients, however, we anticipate that MOH can be managed on an outpatient basis.

Consideration of an appropriate preventive agent

For patients who have more than four headache days per month, and for all patients who are overusing their acute analgesia, a preventive therapy should be considered in addition to stopping the offending medication.[6] There are several resources that provide information on preventive therapy for migraine.[8,9] It is important to trial preventive therapies at a reasonable dose for eight to 12 weeks. As discussed above, because of the maladaptive processes, withdrawal of the offending agent gives patients the best chance to find the right preventer medication for them.

As with all headaches, it is also vitally important to address other reversible and lifestyle factors, such as inadequate water intake, sleep deprivation, high stress levels, sustained poor posture, eye strain from prolonged use of screens, teeth grinding and lack of exercise.

When to refer

Taking the steps above, and starting a preventive agent in complex cases, is helpful for all patients with MOH, even if specialist referral is required, as it gives the specialist a helpful base from which to work. Once MOH has been addressed and treated, patients who did not previously respond to symptomatic or preventer treatments may find them to be effective again.[2] Early referral and input from a specialist may be useful for particular patient groups, such as those:

Table 2. Medications to use as bridging therapy for medication overuse headache

Medication	Suggested dose
Naproxen, sustained release	750 mg orally daily for 5 days, then daily for 3 to 4 days, then cease
Prednisolone	50 mg orally daily for 3 days, then wean over 7 days, then cease

- with complex or multiple pain conditions, symptoms of dependence or high opioid use who may benefit from referral to a multidisciplinary chronic pain service or pain specialist
- with MOH who have not responded to the steps above who may benefit from referral to a neurologist.

A neurologist can also be helpful for patients with migraine who have failed to respond, or have a contraindication, to three lines of oral preventer therapy. These patients can be considered for use of advanced preventer therapies such as botulinum toxin type A or calcitonin gene-related peptide (CGRP) antagonists.[10,11]

Overall, prevention of MOH is better than cure. All acute pain medications can cause MOH. However, there is some evidence that the recently introduced oral small-molecule CGRP antagonists (the gepants, e.g. rimegepant and atogepant) may not cause MOH; therefore, patients who require frequent acute therapy (e.g. with triptans) may benefit from using gepants instead.[12,13] Gepants are not yet PBS subsidised in Australia, so this approach is currently not financially viable for most patients.

As the management of MOH may be complex, a multidisciplinary approach involving GPs, community pharmacists, nurses and allied healthcare providers, with referral to neurologists or headache specialists (where available) for complex cases, is beneficial.[14]

Conclusion

It is important to be vigilant about the frequency and doses of acute medications used in patients with migraine to diagnose and treat MOH in a timely fashion. All patients with primary headaches are at risk of MOH so should have their use of acute medications checked periodically, even if their background therapy with preventers has not changed over years. By adopting a diligent approach, even in patients whose medication lists have not changed over time, we can ensure that the doses of these medications fall into a safe use pattern. **PMT**

References

A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2025/july/supplements/focus-headache-collection).

COMPETING INTERESTS: Professor Stark has served on advisory boards for Teva, Eli Lilly, AbbVie, Viatris and Lundbeck; and received payment for educational presentations from AbbVie, Teva, Eli Lilly and Viatris. Dr Ray has received honoraria for education presentations for AbbVie, Novartis and Viatris, has served on medical advisory boards for Pfizer, Viatris and Lilly, and his institution has received funding for research grants, clinical trials and projects supported by the International Headache Society, Brain Foundation, Lundbeck, Abbvie, Pfizer and Aeon. Dr Gunasekera: None.

MedicineToday 2025; 26(1 Suppl): 38-40
First published in Pain Management Today 2024; 11(1): 66-69
Updated July 2025

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LAKSHINI GUNASEKERA BBMed, MD, FRACP; **JASON C. RAY** MB BS, FRACP, PhD
RICHARD STARK MB BS, FRACP, MACLM

References

1. Headache Classification Committee of the International Headache Society (2018). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 38: 1-211.
2. Sun-Edelstein C, Rapoport AM, Rattanawong W, et al. The evolution of medication overuse headache: history, pathophysiology and clinical update. CNS Drugs 2021; 35: 545-565.
3. Russell MB. Epidemiology and management of medication-overuse headache in the general population. Neurol Sci 2019; 40(Suppl 1): 23-26.
4. Wijeratne T, Jenkins B, Stark RJ, et al. Assessing and managing medication overuse headache in Australian clinical practice. BMJ Neurol Open 2023; 5: e000418.
5. Williams D. Medication overuse headache. Aust Prescr 2005; 28: 59-62.
6. Diener HC, Antonaci F, Braschinsky M, et al. European academy of neurology guideline on the management of medication-overuse headache. Eur J Neurol 2020; 27: 1102-1116.
7. Ray JC, Cheng S, Tsan K, et al. Intravenous lidocaine and ketamine infusions for headache disorders: a retrospective cohort study. Front Neurol 2022; 13: 842082.
8. Prophylaxis for migraine. In: Therapeutic Guidelines, Melbourne. Therapeutic Guidelines Limited; 2019. Available online at: https://www.tg.org.au (accessed July 2024).
9. Ray JC, Macindoe C, Ginevra M, Hutton EJ. The state of migraine: an update on current and emerging treatments. Aust J Gen Pract 2021; 50: 915-921.
10. Ray JC, Kapoor M, Stark RJ, et al. Calcitonin gene related peptide in migraine: current therapeutics, future implications and potential off-target effects. J Neurol Neurosurg Psychiatry 2021; 92: 1325-1334.
11. Ray JC, Hutton EJ, Matharu M. Onabotulinumtoxin A in migraine: a review of the literature and factors associated with efficacy. J Clin Med 2021; 10: 2898.
12. Cheng T, Ray JC, Hilliard T, Stark RJ. Rimegepant – a new oral migraine medication. Med Today 2024; 25(1-2): 35-37.
13. Holland PR, Saengjaroentham C, Sureda-Gibert P, Strother L. Medication overuse headache: divergent effects of new acute antimigraine drugs. Cephalalgia 2020; 40: 889-891
14. Van Driel ML, Anderson E, McGuire TM, Stark R. Medication overuse headache: strategies for prevention and treatment using a multidisciplinary approach. Hong Kong Med J 2018; 24: 617-622.