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DOI:
10.1038/s41433-021-01421-4

Document Version
Peer reviewed version

Citation for published version (Harvard):
Mollan, S, Virdee, J, Bilton, E, Thaller, M, Krishan, A & Sinclair, A 2021, 'Headache for ophthalmologists: current advances in headache understanding and management', *Eye*, vol. 35, no. 6, pp. 1574-1586. https://doi.org/10.1038/s41433-021-01421-4

Headache for ophthalmologists: current advances in headache understanding and management

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Corresponding Author: Alex Sinclair takes full responsibility for the review and interpretation, and the conduct of the research. Alex Sinclair has full access to all of the data.

Declarations or Conflicts of Interest

SPM. – Novartis, speaker fees (2020). Invex therapeutics, advisory board (2020)

ASJ - Novartis and Allergan Advisory board. Speaker fees Novartis. Invex therapeutics, company director with salary and stock options (2019, 2020)

No other authors contributing have a conflict of interest in the subject matter.

Funding

AJS is funded by a Sir Jules Thorn Award for Biomedical Science.

Contributorship Statement

Mollan SP (Neuro-Ophthalmology): Literature review; drafting and review of the manuscript.

Virdee JS (Ophthalmology): Literature review; drafting and review of the manuscript.

Bilton EJ (Medicine): Literature review; drafting and review of the manuscript.

Thaller M (Neurology): Literature review; drafting and review of the manuscript.

Krishnan A (Neurology): Concept and critical review of the manuscript.

Sinclair AJ: Concept and critical review of the manuscript.

All authors read and approved the final manuscript.

Key words: Headache; migraine; medication overuse headache; transient visual obscuration; amaurosis fugax

The following research material is original in nature and has not been submitted to another party whilst under consideration for publication in Eye.

ABSTRACT

Patients with headache and head pain are often referred to ophthalmologists. These symptoms can either be associated with underlying ophthalmic conditions, or more often are headache disorders unrelated to the eyes. Understanding the phenotype of the headache is critical for advice, safe discharge or onward referral. This review will provide an update on the criteria for common headache disorders that are often seen by ophthalmology and embrace disorders associated with ophthalmic diseases. It will also describe the changing management of migraine and outline recent therapies that are currently available.

INTRODUCTION

Headache is very common. The World Health Organisation (WHO) estimates that over half of the global population will have had at least one headache during the past year and within the adult population up to 47% have a general headache disorder [1, 2, 3]. Migraine is the commonest primary headache disorder and is ranked the 2nd most disabling disease globally [4]. It is a costly condition both for the individual [5] and the impact on society [6]. The WHO have stated that headaches are under-treated, under-recognised and under-reported [3].

With increasing frequency, eye care professionals are being referred people with headache to rule out sinister causes of headache, such as papilloedema [7]. However, certain headache disorders can themselves present with visual disturbances or autonomic features such as engorged conjunctival vessels or a watery eye. Headache may be a key clinical feature of ophthalmic conditions such as idiopathic intracranial hypertension (IIH) [8]. This review will provide an informed appraisal consistent with the International Headache Society (IHS) criteria for common headaches that frequently present to ophthalmology and present the new advances in the management of migraine.

111

112 **APPROACHING HEADACHE**

113 Headache is typically classified into primary headache
114 disorders, secondary headache disorders and facial pains or
115 neuralgias. Each headache has been classified by the
116 International Headache Society Classification Criteria (ICHD-3)
117 which are routinely updated for accuracy [9]. The National
118 Institute for Clinical Excellence (NICE) (2012) and the British
119 Association for the Study of Headache (BASH) have produced
120 guidelines on the assessment of headache and consideration of
121 onward referral in patients [10, 11]. The aetiology of primary
122 headache disorders is more elusive than secondary headaches,
123 which are headache arising from a defined cause. The previous
124 concept that migraine was caused by rebound dilatation of
125 constricted blood vessels in the brain, which was developed by
126 Wolff in the 20th Century, is no longer accepted [12]. Migraine
127 is felt to be primarily a neuronal issue, driven by
128 trigeminovascular activation [13, 14]. Headaches can also arise
129 from traction to the meninges and blood vessels, such as in a
130 space occupying lesion, and through inflammation/infection of
131 the meninges [15].

132

133 Pathophysiology in headaches has been extensively studied,
134 but still poorly understood, and a wide variety of mechanisms

135 have been proposed, such as plasma protein extravasation and
136 inflammation, release of neuropeptides such as Calcitonin
137 gene-related peptide (CGRP), neuronal sensitisation leading to
138 features such as allodynia, specific central connections and
139 higher order processing [16].
140
141 Migraine is by far the commonest primary headache disorder
142 seen, followed by tension headache and then less common
143 disorders such as trigeminal autonomic cephalalgias (such as
144 cluster headache). Secondary headache disorders have an
145 underlying aetiology that likely requires active management
146 and include structural (such as Chiari malformation), trauma,
147 infection, neoplasia, vascular causes or raised intracranial
148 pressure.
149
150 Key elements to note in the headache history will help
151 distinguish, to a certain degree, the underlying headache
152 phenotype. Severity of pain can either be documented on a
153 verbal rating scale by the patient (for example between 0 being
154 no pain and 10 being the worst pain); duration of pain; how
155 often the pain occurs; location of the pain; nature of the pain
156 (such as throbbing, pulsing or stabbing); were there prodromal
157 features, occurrence of aura (visual, sensory or motor aura or
158 speech disturbance); during the headache were there

159 associated features of photophobia, phonophobia;
160 osmophobia; nausea or vomiting; aggravation by physical
161 activity. Determining the headache frequency helps distinguish
162 disorders, and prepares for target management plans. A
163 summary of the headache phenotypes and key diagnostic
164 criteria and phenotypes are detailed in Table 1 and Table 2
165 (adapted from ICHD-3 and NICE CKS) [9, 17].
166
167 **RED FLAGS**
168 There are red flags that may require immediate or urgent
169 investigation, particularly where there may be a secondary
170 cause of the headache. They include new severe, unexpected
171 headache, progressive or persistent headache which has
172 changed dramatically, fever/impaired consciousness,
173 papilloedema, new neurological deficit, features of giant cell
174 arteritis, change in personality, dizziness, visual symptoms,
175 vomiting [17]. The box below has been adapted from the
176 headache red flag mnemonic "SNOOPS", which has been
177 described in 2003 and taught to medical students around the
178 world as an aide memoire for identifying suspicious features in
179 a patient presenting with headache [18, 19]. Updated
180 guidelines have led to the formation of the current SNOOP10
181 mnemonic in 2018 [19]. This has a more comprehensive list of
182 ten 'P's – which include: pattern change/recent onset of

183 headache, positional headache, precipitated by
184 coughing/sneezing, papilloedema, progressive headache,
185 pregnancy/puerperium, painful eye with autonomic features,
186 posttraumatic onset, pathology of immune system, painkiller
187 overuse or new drug at onset of headache (Box 1).
188
189 There is a temptation for clinicians and patients to elect for
190 routine neuro-imaging for reassurance when headache is a
191 principle symptom for a consultation. However, this is not
192 recommended by NICE [17]. Incidental findings are common,
193 up to 2.7% in one study, however they did not include white
194 matter hyperintensities, silent brain infarcts, brain microbleeds,
195 and anatomical variants. They also did not include the
196 difference in fidelity between 1.5 and 3.0 Tesla (T) MRI
197 scanners, where the incidence seen within a 3T scanner may be
198 much higher. Benign pathology can cause significant concern
199 for the patient, and the non-specialist [20]. Indications for
200 imaging include where there are atypical features and/or
201 abnormal clinical signs on examination suggesting an
202 alternative underlying cause of the headache (Box 1).
203
204 **VISUAL DISTURBANCES ASSOCIATED WITH HEADACHE AND**
205 **PAIN**

206 Visual disturbances within in the context of head and eye pain
207 can be wide ranging and include amaurosis fugax, Uhthoff's
208 phenomenon, transient visual obscuration and visual aura
209 (Table 3). Taking an accurate history of both the visual
210 disturbance and headache can aid in formulating a robust
211 differential diagnosis and management plan for workup and
212 treatment.
213
214 Monocular transient visual loss (TVL) or amaurosis fugax is
215 usually a medical emergency. There is interrupted blood flow
216 to the central retinal/ophthalmic artery causing the symptom
217 of a blackout in the whole or half of the visual field, possibly
218 starting with a "curtain" sweeping in from one side of the vision.
219 This is temporary and typically resolves within minutes and lasts
220 no longer than one hour. It can be caused by thromboembolism
221 originating from an atherosclerotic plaque in the internal
222 carotid artery, or an embolus originating from the heart or
223 aorta. If associated with atheromatous carotid artery disease
224 there is a 2% risk of recurrent stroke at one year and in those
225 with severe internal carotid artery stenosis, the risk of
226 ipsilateral stroke is up to 16% after three years [21]. An embolus
227 can also originate from a carotid artery dissection. Giant cell
228 arteritis (GCA) is another serious cause of TVL that can be
229 associated with headache [22, 23]. Differentiating between TVL

230 caused by migraine aura or transient ischaemic attack (TIA) is
231 challenging, particularly in the ≥60 years old age group where
232 TIA's become more common and migraine with aura attacks
233 become more atypical in nature [24].
234
235 Transient greying or blacking out in the vision, which may occur
236 when a patient moves/bends down, define transient visual
237 obscurations. These can occur in optic nerve swelling and
238 papilloedema, typically last seconds before the vision returning
239 to normal [25, 26].
240
241 The Uhthoff phenomenon is a symptom, typically associated
242 with a blurring of the vision occurring after physical exercise or
243 activities that increase in body temperature, e.g. after a hot
244 shower or bath [27, 28]. It occurs in association with optic
245 neuritis, either as a clinically isolated syndrome or within the
246 context of diagnosed demyelinating disorders such as multiple
247 sclerosis and neuromyelitis optica spectrum disorder. It is
248 thought that increased temperature prolongs inactivation
249 of voltage-gated sodium channels and therefore increases the
250 chance of conduction failure in partially myelinated or
251 incompletely remyelinated axons.
252

Current thinking suggests cortical spreading depression is the underlying pathophysiology of visual aura [13]. The typical clinical history suggests it develops gradually over 5-20 minutes and last for less than 60 minutes. It starts in the periphery and there may be a positive scotoma. Migraineurs describe many different symptoms that include phosphenes, and more complex visual hallucinations of fortifications of flashes of light, zigzags, scintillating scotomas and visual illusions like teleopsia or metamorphopsia [29, 30].

Visual disturbances in nonconvulsive epilepsy can be difficult to distinguish from migraine aura and can cause a diagnostic dilemma. One small case series found the localization and patterns of the symptoms can differ between the two. In epilepsy, positive visual phenomena were centrally located in the visual field of epileptic patients and peripheral in those with migraine. Negative visual phenomena tended to be diffuse in epilepsy and peripheral in migraine aura [31]. The duration of symptoms in epilepsy tended to be extremely short lasting a few seconds whereas discussed migraine aura lasts between 5 and 60 minutes. The presence or absence of color does not distinguish the two conditions. Where there is diagnostic confusion an EEG may be helpful in determining the diagnosis.

MIGRAINE

For the diagnosis of migraine to be upheld the IHS have set criteria (ICHD-3), detailed in Table 1 [9, 17].

It is now accepted that there are premonitory symptoms that can occur days before the headache onset. The most commonly reported premonitory symptom is marked fatigue that has been shown to be highly predictive of an ensuing migraine attack [32]. Other premonitory symptoms include mood change, anxiety, irritability, unhappiness, yawning, asthenia, gastrointestinal disturbance, change in appetite, muscle aches, hypersensitivity to light/sounds, difficulty concentrating and confusion [33, 34].

Migraine is also noted to have a phenotypic postdrome, which can be broadly grouped into four areas – neuropsychiatric, sensory, gastrointestinal and general systemic symptoms. These range from fatigue, difficulty concentrating, excessive yawning, to photophobia, nausea, difficulty with speech and/or writing [35]. These often appear quite similar to the premonitory symptoms and it is theorised that therefore they may share a common neural network [36].

AURA

Aura is defined as a fully reversible cluster of neurological symptoms. Symptoms often spread gradually over 5 or more minutes and should resolve fully within 60 minutes of onset [9]. Aura is experienced in 25-30% of sufferers [37]. Aura may include visual symptoms (as described above), difficulty with speech, paraesthesia, allodynia, confusion, and heightened sense of smells [38].

It has been observed that patients who suffer from active migraine with aura are associated with increased risk of major cardiovascular disease (CVD), myocardial infarction, ischemic stroke, and death due to ischemic CVD [39, 40]. Thus increased risk of ischaemic stroke is associated with migraine with aura, young age, female sex, use of oral contraceptives and smoking habits [41]. With regards to contraception, as many migraine sufferers are female of childbearing age, it must be carefully considered if their headache is typical of migraine before recommending contraceptive changes. The WHO state that the use of combination estrogen/progesterone contraception may be considered for women with migraine headache only if they do not experience aura, do not smoke, are otherwise healthy, and are younger than age 35 years [42]. Otherwise, patients should not take oral combined contraceptive pill. The progesterone only pill is safer and not associated with increased

stroke risk. Other options include oral desogestrel; the subcutaneous implant etonogestrel; the injection medroxyprogesterone acetate or an intrauterine device such as levonorgestrel.

The risk of stroke is increased by smoking, migraine type and use of hormonal contraception (Box 2) and a consensus statement was made in 2017 by the European Headache Federation and the European Society for Contraception and Reproductive Health [43].

EPISODIC TO CHRONIC MIGRAINE

Headache frequency can broadly classify migraine into two types: episodic migraine (less than 15 headache days per month) or chronic migraine (15 or greater headache days per month). The International Classification of Headache Disorders 3rd edition Appendix A1.3 defines chronic migraine as greater than or equal to 15 headache days per month for at least 3 months, with at least 8 days per month fulfilling criteria for migraine without aura, in the absence of medication overuse and that cannot be attributed to another causative disorder [9]. Headache frequency is variable and changes over time. Chronic migraine often begins as episodic which increases and worsens in frequency and is often associated with concurrent tension

348 type headache [44]. The yearly incidence of chronic migraine
349 from episodic migraine is 2.5% [45]. Refractory migraine is
350 defined by having failed all of the available preventatives and
351 suffer from at least 8 debilitating headache days per month for
352 at least 6 consecutive months. Migraine has significant financial
353 burden which has been shown across five European countries
354 from the International Burden of Migraine Study 2012 [46]. It
355 showed chronic migraine was associated with greater
356 healthcare cost than episodic migraine, more provider visits,
357 emergency department/hospital visits, and diagnostic tests and
358 three times higher medical costs [46].
359
360 **TRIGEMINAL AUTONOMIC CEPHALAGIAS**
361 Trigeminal autonomic cephalalgias (TACs) are characterised by
362 strictly unilateral nature, ipsilateral cranial autonomic
363 symptoms and their severity. This group includes Cluster
364 Headache, Paroxysmal Hemicrania, Short-lasting Unilateral
365 Neuralgiform attacks with Conjunctival injection and Tearing
366 (SUNCT) and Short-lasting Unilateral Neuralgiform attacks with
367 cranial autonomic symptoms (SUNA).
368
369 **CLUSTER HEADACHE**
370 Cluster headache is a primary headache disorder affecting up
371 to 0.1% of the population. It is often misdiagnosed, as those

with cluster attacks may seek advice of dentists or indeed eye care professionals. The pathophysiology involves activation of the trigeminovascular complex and the trigeminal-autonomic reflex. There is severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting between 15 minutes and 2 hours [47]. The attacks can include autonomic symptoms such as ipsilateral conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhoea; eyelid oedema; forehead and facial sweating; forehead and facial flushing; sensation of fullness in the ear; or miosis. Those with cluster describe a sense of restlessness or agitation. The attacks can happen up to 8 times a day [48]. It is more common in males with a 2.5 male to 1 female ratio [48]. Cluster attacks can be triggered by strong smells and by ingestion of alcohol (with onset within minutes). The first line acute treatments are high flow oxygen or sumatriptan (nasal or subcutaneous).

Hemicrania continua has recently been added to the TACs. [49] Paroxysmal Hemicrania attacks are shorter than Cluster headache (2-30 min) and frequency is above 5/day on the majority of episodes. The key to differentiation is the complete response to therapeutic dose to indomethacin (initially at least 150mg daily). Similarly Hemicrania Continua has absolute response to indomethacin but it is continually present for more

than 3 months with exacerbations of moderate-high intensity with associated agitation. The differentiation between SUNCT and SUNA is which autonomic features are present. The SUNCT and SUNA peaks are much shorter lasting 1-600 seconds as single stabs, groups of stabs or a sawtooth pattern. Multiple cutaneous stimuli have been reported to trigger attacks.[50] They do not have the response to indomethacin that is characteristic of the Hemicranias.

OCULAR CONDITIONS THAT MASQUERADE AS PRIMARY HEADACHE DISORDERS

The primary headache disorders can mimic many ocular diseases. The pain can be located periorbital and retroorbital and when associated autonomic features such as conjunctival injection, lacrimation, mild ptosis and eyelid oedema. An ophthalmic examination is important in all new onset cases where there are unexplained ophthalmic symptoms or signs. Not infrequently our non-ophthalmic colleagues can mistake sub-acute and acute angle closure as a headache disorder, particularly if the symptoms are episodic and insidious [51]. Similarly in uveitis and scleritis with pain and photophobia, can be misdiagnosed as although some are easily differentiated with a slit-lamp examination, conditions such as posterior scleritis are not [52].

A diagnosis that requires careful investigation is ophthalmoplegic migraine. It is a rare and is characterized by recurrent bouts of head pain and ophthalmoplegia. The third cranial nerve is most commonly affected. Most patients recover completely within days to weeks, but a minority are left with persistent neurologic deficits.[53]

SECONDARY HEADACHES

Secondary headaches are headaches caused by another medical disorder, and are recognised by the International Classification of Headache Disorders, 3rd edition, and have to fulfil specific criteria, such as a clear temporal relationship between the disease process and headache symptoms, a clear correlation of patient symptoms and symptoms expected in this disease and improvement of headache with improvement of the underlying disease [9]. Headaches may be attributed to a number of different causes that may present acutely to ophthalmology include trauma to the head or neck that may cause a Horner Syndrome, intracranial tumours such as pituitary apoplexy, intracranial haemorrhage from aneurysmal causes, arteriovenous malformations causing visual field disturbances and carotid cavernous fistulas.

444 In the ophthalmology clinic, there are several key secondary
445 headaches that require active timely investigation and
446 management such as giant cell arteritis, pituitary apoplexy,
447 raised intracranial pressure, and idiopathic intracranial
448 hypertension (IIH).
449
450 **GIANT CELL ARTERITIS**
451 New onset headache is a cardinal symptom of GCA, with 67%
452 reporting this symptom [54]. The IHS definition of headache
453 attributable to GCA is a classification system, rather than
454 diagnostic criteria [9]. Caution needs to be applied as
455 improvement in headache with high dose glucocorticoids
456 happens in many secondary headaches, not just those
457 attributable to GCA. The GCA headache characteristics are
458 poorly defined in the literature with few investigating the
459 headache phenotype systematically [22, 23]. It has been
460 reported as continuous in 60% with just under half having
461 paroxysmal headache [55]. Case reports suggest that the
462 headache is severe and unlike prior headaches in those who
463 have had a prior history of headache [56]. However, there is a
464 spectrum of severity of the pain, and one series reported a
465 range from severe (42%), to moderate (37%) and mild (21%)
466 [55]. The location of pain is commonly reported in the temporal
467 artery (TA) region, when the TA is involved and may be more

468 holocranial in nature in others, likely dependent on the arterial
469 involvement of the disease [57]. In one small series nineteen
470 cases at a Japanese headache centre reported, as expected, the
471 location of the headache to be temporal [55]. Headache has
472 also being reported to be a common symptom at relapse [58].
473 The GCA headache phenotype is yet to be fully differentiated.
474 Where headache does not markedly improve on starting
475 glucocorticoids, this should be considered a red flag and an
476 alternative diagnosis to GCA considered.
477
478 **PITUITARY APOPLEXY**
479 Characterized by infarction or haemorrhage of the pituitary
480 gland leading to localised oedema or bleeding, pituitary
481 apoplexy (PA) is a potentially fatal endocrinological emergency.
482 The majority of PA cases are found to have a co-existent
483 pituitary adenoma, 80% of which were undiagnosed prior to the
484 development of apoplexy [59].
485 PA presents as a clinical syndrome of acute or subacute
486 headache, vomiting, visual impairment, and decreased
487 consciousness [60]. Sudden onset headache is the most
488 frequent presenting feature, present in 80-93% of patients [61,
489 62, 63]. The characteristics of PA headache are variable.
490 Unilateral frontal headache is most common but retro-orbital,
491 bifrontal, diffuse, temporal, thunderclap and occipital

492 headaches are also recorded in the literature [61, 62]. Vomiting
493 is present in just over half of cases [62]. Visual abnormalities
494 can include loss of visual acuity, cranial nerve palsies III, IV and
495 VI and visual field loss, most commonly bitemporal
496 hemianopsia [64]. Pituitary insufficiency is also a common
497 finding, with corticotropic deficiency present in 50-80% of cases
498 [61].
499 Although part of the clinical syndrome, the cardinal symptoms
500 can be present infrequently and may not co-exist with each
501 other, with reports of PA presenting initially as isolated cranial
502 nerve palsies without, or prior to, the development of headache
503 [65, 66].
504 Due to the highly variable presentation of PA, differentiation
505 from other important diagnoses such as subarachnoid
506 haemorrhage or meningism is often difficult if the
507 pathognomonic features are absent. As such CT head imaging is
508 often performed prior to MRI even though the latter is known
509 to have higher sensitivity to detect acute intrasellar
510 haemorrhage or infarction [67].
511
512 **CAVERNOUS SINUS SYNDROME**
513 This syndrome is caused by any pathology in the cavernous
514 sinus which causes disruption to its contents, resulting in
515 characteristic symptoms and signs. Causes include tumours

516 such as meningioma, inflammatory disease such as sarcoidosis,
517 trauma, vascular lesions such as intracavernous aneurysm and
518 carotid-cavernous fistula; and infections such as aspergillosis.
519 [68] Commonly there is new onset headache in combination to
520 clinical examination findings such as; ophthalmoplegia – as the
521 cavernous sinus transmits cranial nerves 3, 4 and 6; corneal and
522 facial sensory loss, due to cranial nerve 5a and b involvement;
523 Horner syndrome; proptosis and chemosis.
524
525 Vascular lesions such as a carotid-cavernous fistula can present
526 with pain. Direct fistulas are often a result of head trauma, and
527 indirect are often spontaneous and related to atherosclerosis.
528 In addition to the signs listed above, there may be an orbital
529 bruit, increased intraocular pressure, and engorgement
530 "arterialisation" of the conjunctival vessels and a relative
531 afferent pupillary defect [69]. When suspected the workup
532 should be done urgently, and usually a combination of blood
533 tests for infection/inflammatory markers and directed
534 neuroimaging confirms the fistula.
535
536 **IDIOPATHIC INTRACRANIAL HYPERTENSION**
537 Idiopathic Intracranial Hypertension (IIH) is characterized by an
538 elevation of intracranial pressure (ICP) with no identifiable
539 cause [70]. There is a rising incidence in this disease [71], it

typically affects women of working age [72] and headache is the predominant morbidity in over 90% [73]. Headache is also the key factor driving reduced quality of life in IIH [74]. Previous characterization of the typical phenotype of a raised intracranial pressure headache was of a nonspecific headache that is worse on waking [7]. The IIH Treatment Trial (IIHTT) characterised IIH headache in their participants as pressure-like in 47% and throbbing 42%, which is similar to migraine [75]. Photophobia, phonophobia, nausea, vomiting, and worsening on physical activity were reported and none of these migraine features separated IIH headache from migraine [75]. Headache severity in IIH appears to be moderate to severe [76]. Headache frequency in IIH appears to be typically episodic in new onset disease and chronic in more longstanding disease [8]. In the IIHTT, both severity and frequency have not appeared to correlate with CSF opening pressure [75], this may seem counterintuitive but may reflect as a rare disease the numbers needed to find significance is challenging. As the predominant phenotype of headache in IIH is migrainous, the consensus guidelines suggested a practical approach of using abortive and preventative migraine therapies, with the caution of avoiding those medications with side-effects of weight gain [76]. There have been no trials specifically investigating the management of headache in IIH [77]. A recent open label study of 55 patients

564 with IIH in ocular remission (resolved papilloedema) and
565 chronic migraine-like headaches investigated the use of
566 erenumab, a calcitonin gene-related peptide monoclonal
567 antibody. Erenumab reduced the frequency of
568 moderate/severe headache days by 71% and all headache days
569 by 45% from baseline to 12 months. Further, Erenumab
570 significantly increased crystal clear days, reduced analgesic
571 days, reduced severity and reduced absenteeism and
572 presenteeism.[78] A key clinical point from was that treating
573 the headache successfully, then abolished headache as a
574 cardinal symptom of recurrence of disease. This was evidenced
575 by seven patients who had recurrence of papilloedema without
576 headache, suggesting that patients should be warned regarding
577 weight gain, and need to be reassessed by ophthalmology
578 should this occur.[79]
579
580 **MEDICATION OVERUSE HEADACHE**
581 Medication overuse headache (MOH) is a treatable
582 phenomenon because the specific treatments that patients
583 take to control headaches actually cause headache. MOH
584 patients often present with chronic headache were the MOH
585 can mask the underlying phenotype of the original headache
586 disorder, making them a diagnostic challenge. There is also
587 evidence that overuse of barbiturates and opiates, but not

triptans, has been associated with increased risk of progression from episodic migraine to chronic migraine [80].

ICHD-3 defines MOH diagnostic criteria as having: headache present on greater than 15 days/month, regular overuse for greater than 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, headache has developed or markedly worsened during medication overuse [9].

The commonest medications causing MOH are paracetamol, opioids, aspirin, triptans and NSAIDs. Bigal *et al*. in 2004 defined medication overuse defined according to the analgesic that is being used [81]:

1. Simple analgesic use (>1000mg ASA/acetaminophen/paracetamol) >5 days/week;
2. Combination analgesics use (caffeine containing) >3 tablets a day for >3 days a week;
3. Opiate use >1 tablet a day for >2 days a week;
4. Ergotamine tartrate use: 1 mg PO or 0.5 mg PR for >2 days a week.
5. Triptans: overuse >1 tablet per day for >5 days per week.

612

613 Patients should be counselled and warned about the risks of
614 MOH [82]. Addressing MOH is medication specific for example
615 drugs such as triptans and NSAIDs can be stopped abruptly;
616 patients should aim to stop taking the offending drug for at
617 least 1 month. Abrupt withdrawal may precipitate withdrawal
618 headache which lasts on average 3.5 days but can be up to 10
619 days. Other withdrawal symptoms may include gastrointestinal
620 such as nausea and vomiting, cardiovascular such as
621 hypotension, tachycardia, neuropsychiatric such as sleep
622 disturbances, restlessness, with autonomic overly and can
623 include anxiety and nervousness [83]. The drug overused is
624 responsible for the time taken to improve - triptans or ergots
625 approximately take 7-10 days and simple analgesics 2-3 weeks
626 [83].

627

628 The original headache disorder is elicited usually within 2
629 months of cessation of analgesics. If relapse occurs, behavioural
630 therapy and stress management techniques can be considered.
631 Patients should be provided with written information on
632 “Painkiller headaches” so that they may understand the process
633 and increase compliance with the management plan [82].

634

635 It is also worth considering that MOH is a presumed diagnosis
636 and withdrawing medication may not help the headache, in
637 which case further workup is indicated to reach the diagnosis
638 [83].
639
640 **MANAGEMENT OF MIGRAINE**
641 Management of headache aims for effective control of
642 symptoms. Migraine is life-long condition and a cure is
643 unrealistic. The WHO reflected that migraine is under treated
644 [3], and under treated headaches are not cost effective as they
645 cause unnecessary pain, reduce an individual's productivity and
646 led to repeated medical consultations. There are two targets for
647 head pain: acute therapies, which may be non-specific or
648 specific, and preventative treatments. The choice is largely
649 dependent on the frequency of the headache. Lifestyle advice
650 should be given with all headache disorders, as these can have
651 considerable impact on the disease course. Strategies should be
652 implemented to limit caffeine intake, ensure regular meals and
653 adequate hydration, an exercise program and sleep hygiene.
654 Behavioural and stress management techniques can be
655 implemented such as yoga, cognitive behavioural therapy and
656 mindfulness. Of particular note, there are no currently
657 treatments for aura although a number of treatments have

658 been investigated, often in case series or un-blinded studies,
659 none have proven to be of clinical benefit.
660
661 **ABORTIVE THERAPIES**
662 These includes non-specific drugs (analgesics and non-steroidal
663 anti-inflammatory drugs—NSAIDs) and specific drugs (ergot
664 derivatives and triptans) [84]. Opiates should be avoided due to
665 the risk of MOH and dependency.
666 Specific combination therapy should be offered first line,
667 usually an oral triptan (e.g. sumatriptan 50mg) and an NSAID,
668 or an oral triptan and paracetamol, some are available in melt
669 preparations which dissolve under the tongue for faster action.
670 If the patient prefers monotherapy, this could be either a
671 triptan, NSAID or aspirin (high dose – 900mg 4-6 hourly,
672 maximum dose 4g daily). An antiemetic can be considered even
673 if nausea and vomiting are not present. Importantly opioids or
674 ergots are not to be prescribed.
675
676 Triptans are selective 5-hydroxytryptamine (5HT) receptor
677 agonists, with affinity for the 5HT1B and 5HT1D receptors.
678 5HT1B receptors are on blood vessels smooth muscle cells and
679 cause vasoconstriction when stimulated. 5HT1D receptors
680 occur on perivascular trigeminal nerve terminals and in the
681 dorsal horn, with activation blocking peptides from the

682 trigeminal and neurotransmitter release in the dorsal horn that
683 convey nociceptive information to the thalamus [85].
684 Commercially, seven triptans are available—sumatriptan,
685 rizatriptan, eletriptan, naratriptan, zolmitriptan, frovatriptan,
686 and almotriptan — with minor differences in
687 pharmacokinetics/dynamics. The first agent has been used
688 since the 1990s. These medications are contraindicated in
689 coronary artery disease, cerebrovascular disease, peripheral
690 vascular disease, and uncontrolled hypertension. Side effects
691 can occur, and include dizziness, drowsiness, dyspnoea,
692 flushing, myalgia, nausea pain, temperature sensation altered,
693 vomiting, angina pectoris, anxiety, arrhythmias, arthralgia,
694 colitis, ischaemic coronary vasospasm, diarrhoea, dystonia,
695 hyperhidrosis, hypotension, myocardial infarction, nystagmus,
696 palpitations, Raynaud's phenomenon, seizure, tremor and
697 vision disorders. Triptans can be taken orally, nasally and
698 subcutaneously. Sumatriptan subcutaneous and nasal
699 preparations have faster onset of action (within 15 minutes),
700 whereas oral tablets generally take longer to work (30-60
701 minutes). Patients should not take ergotamine within 24 hours
702 nor monoamine oxidase inhibitors within 14 days of taking
703 triptans. NICE found that overall, triptan plus NSAID
704 combination therapy was ranked the most cost-effective

705 treatment, followed by triptan plus paracetamol, and then
706 triptan monotherapy [10].
707
708 New classes of acute abortive treatments are emerging with
709 ditans and gepants (see below) but widespread availability is
710 currently limited. Lasmiditan offers therapeutic efficacy but
711 dizziness can compromise driving acutely [86, 87, 88].
712
713 **PREVENTATIVE THERAPIES**
714 The aim of preventive treatment is to reduce the frequency,
715 severity, and duration of migraine attacks, and avoid
716 medication-overuse headache [47]. This is usually considered if
717 migraines are causing disability regularly, for example, if there
718 are two or more attacks per month that produce disability
719 lasting for 3 days or more [10]. The majority of migraine
720 preventative treatments are repurposed medications such as
721 topiramate and propranolol. These are taken daily. Propranolol
722 is also useful for treating co-existent anxiety and hypertension.
723 Riboflavin taken at 400mg once a day can also be useful in
724 reducing migraine frequency. Venlafaxine and angiotensin
725 receptor type 2 antagonists have also been tried.
726
727 **BOTULINUM TOXIN TYPE A (BT-A)/ ONABOTULINUMTOXIN A**

More recently, newer therapies have emerged for the treatment of migraine. NICE have approved Botulinum toxin type A (BT-A) for migraine in specific circumstances. The proposed mechanisms of action are inhibition of muscle spasms aiding headache, a direct or independent and prolonged analgesic action unrelated to skeletal muscle relaxation is believed to underlie the prophylactic efficacy of BT-A in migraine and peripheral and central modulation of pain impulses by BT-A has also been proposed [89].

The NICE eligibility criteria for use of BT-A in migraine are adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine), that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse are eligible. The PREEMPT trials, which compared BT-A with placebo, was analysed by the NICE committee. This showed that the pooled results for the intention-to-treat population indicated a statistically significant reduction in frequency of headache days per month, migraine days per month and cumulative headache hours with BT-A compared with placebo [90]. The main drawback of studies in migraine is the high placebo effect noted in these studies. Treatment with BT-A is longstanding, and many be required for

752 longer than 2 years. Patients need at least two treatment cycles
753 to assess response to BT-A. Subsequently, approximately 50%
754 of people would continue on treatment, 30% would need 5
755 cycles before being classified as episodic migraine. The
756 remaining patients would continue to receive treatment for
757 longer than 2 years. Alternatively, if the patient does not
758 respond to BT-A, this should be discontinued and they should
759 receive standard care. A recent Cochrane review found that in
760 chronic migraine, BT-A may reduce the number of migraine
761 days per month by two days compared with placebo treatment.
762 Non-serious adverse events were probably experienced by
763 60/100 participants in the treated group compared with 47/100
764 in the placebo group [91, 92, 93].
765
766 **NEUROSTIMULATION**
767 Neuromodulation devices are available for headache, which
768 utilise a variety of technologies [94]. Non-invasive stimulation
769 options include supraorbital stimulation (Cefaly), vagus nerve
770 stimulation (gammaCore) and single-pulse transcranial
771 magnetic stimulation (SpringTMS). Invasive procedures include
772 occipital nerve stimulation, sphenopalatine ganglion
773 stimulation and ventral tegmental area deep brain stimulation.
774 Evidence for these therapies is sparse and involve a small
775 number of patients, and often manufacturer-sponsored trials.

776

777 **CALCITONIN GENE-RELATED PEPTIDE (CGRP) THERAPIES**

778 The need for newer treatments is evident because fewer than
779 50% of patients on current pharmacological therapy experience
780 50% reduction in their headache symptoms [95]. Calcitonin
781 gene-related peptide (CGRP) is a neuronal peptide that has
782 been shown to be released during migraine attacks. More than
783 30 years ago CGRP was demonstrated in trigeminal ganglion
784 (TG) pseudounipolar neurons [96]. Two different CGRP blockers
785 have been developed, a small molecule CGRP receptor
786 antagonists and immunoglobulins targeting CGRP or the CGRP
787 receptor. These drugs are generally well tolerated, with the
788 exception that early gepant class drugs had been associated
789 with liver toxicity. CGRP is also found in the vasculature and
790 therefore we can infer that there may be issues in patients with
791 cardiovascular comorbidities.

792 In 2004, a proof-of-concept study showed that intravenous
793 olcegepant (the first calcitonin gene-related peptide (CGRP)
794 receptor antagonist) was effective in the acute treatment of
795 migraine [97]. A number of other gepants for the acute
796 treatment of migraine have been studied including:
797 telcagepant, olcegepant, BI 44370, rimegepant (BMS-927711),
798 MK3207, and ubrogepant, some of which have been shown to
799 be superior to triptans for pain relief at 2 hours [98]. Further

800 direct comparison studies are required to establish further
801 conclusions [98].
802 Antibodies against CGRP or the CGRP receptor have been tested
803 as prophylactic treatment of episodic and chronic migraine.
804 Randomised controlled trials investigating four agents,
805 Erenumab, Fremanezumab, Galcanezumab, Eptinezumab have
806 shown high efficacy in prevention of episodic and chronic
807 migraine [99]. Anti-CGRP monoclonal antibody therapies are
808 becoming increasingly utilised internationally, but in some
809 countries are only funded in those who are treatment
810 refractory.
811
812 **CONCLUSION**
813 Headache represents a very common clinical symptom and can
814 be associated with a wide variety of clinical conditions, some of
815 which can be lethal. It is important to take a thorough history
816 and examination, with a cautious approach, to identify serious
817 pathology. Cranial nerve examination and peripheral
818 neurological examination may be required. Headaches often
819 present to the ophthalmologist with other ophthalmic signs and
820 symptoms and it is important to be aware of the types of visual
821 phenomenon that can be found in conjunction with headache
822 to help to formulate a differential diagnosis. New treatments
823 are available for headache.

824

825 **Summary points for EYE:**

826 **What was known before**

827 1. Headache morbidity is high in the general population.
828 2. The aetiology of headaches may be primary or
829 secondary.
830 3. Medication overuse headache, a preventable entity, can
831 complicate the investigation and management of
832 headache disorders.

833

834 **What is known now**

835 1. Secondary headaches, such as idiopathic intracranial
836 hypertension, mimic migraine-like headaches.
837 2. Botulinum toxin type A for chronic migraine can reduce
838 the number of monthly migraine days by two compared
839 to placebo.
840 3. Therapies targeting calcitonin gene-related peptide
841 (CGRP) have been shown in randomised controlled trials
842 to be safe and effective for both treatment of the acute
843 attack (gepants); and prevention in chronic and episodic
844 migraine (anti-CGRP monoclonal antibodies).

845

846

847

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Table 1: Summary of headache classification adapted from NICE CKS [10]

Headache Type	**Consider if:**
Migraine without aura	At least five attacks fulfilling the following criteria: o Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated). o The 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 (for example walking or climbing stairs). o During the headache at least one of the following; nausea and/or vomiting; photophobia and phonophobia.
Migraine with aura	At least two attacks fulfilling the following criteria: o One or more of the following fully reversible aura symptoms: ▪ Visual symptoms such as zigzag lines and/or scotoma— visual aura is the most common type of aura. ▪ Sensory symptoms such as pins and needles. ▪ Speech and/or language symptoms such as aphasia. ▪ Motor weakness. ▪ Brainstem symptoms such as vertigo or diplopia. ▪ Retinal symptoms such as monocular scintillations or scotoma. o At least two of the following four characteristics: ▪ At least one aura symptom spreads gradually over at least 5 minutes, and/or two or more symptoms occur in succession. ▪ Each individual aura symptom lasts 5-60 minutes. ▪ At least one aura symptom is unilateral. ▪ The aura is accompanied, or followed within 60 minutes, by headache.
Tension-type headache	At least two attacks fulfilling the following criteria: xxx

Cluster headache	At least five attacks of severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes *and* Associated with at least one of: ipsilateral conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhoea; eyelid oedema; forehead and facial sweating; forehead and facial flushing; sensation of fullness in the ear; or miosis *and/or* a sense of restlessness or agitation. Attacks occur between one every other day and eight per day for more than half of the time when the disorder is active.
Medication overuse headache	The person has headache occurring on at least 15 days per month and a pre-existing headache disorder. Regularly overused, for more than 3 months, one or more drugs that can be taken for acute and/or symptomatic treatment of headache such as ergotamines, triptans, simple analgesics or opioids.

Table 2 Typical headache phenotypes

Headache feature	**Tension-type headache**	**Migraine (with or without aura)**	**Cluster headache**
Pain intensity	Mild or moderate	Moderate or severe	Severe or very severe
Pain location	Bilateral	Unilateral or bilateral	Unilateral (around the eye, above eye and along the side of the head/face)
Pain quality	Heavy, pressure, tightening (non-pulsating) Can be featureless	Pulsating	Variable (can be sharp, boring, burning, throbbing or tightening)
Effect on activities	Not aggravated by routine activities of daily living	Aggravated by, or causes avoidance of, routine activities of daily living	Restlessness or agitation
Associated symptoms	None	Photophobia, phonophobia nausea and/or vomiting Aura Typical aura symptoms include visual symptoms and/or partial loss of vision; sensory symptoms such as numbness and/or pins and	Ipsilateral: • hyperaemic and/or watery eye • nasal congestion and/or rhinorrea • Eyelid oedema/swelling • forehead and facial sweating • Miosis/ptosis

			needles; and/or speech disturbance			
Duration of headache	30 minutes–hours		4–72 hours in adults 1–72 hours in young people aged 12–17 years		15–180 minutes	
Frequency of headache	< 15 days per month	≥ 15 days per month for more than 3 months	< 15 days per month	≥ 15 days per month for more than 3 months	1 every other day to 8 per day[3], with remission[4]> 1 month	1 every other day to 8 per day[3], with a continuous remission[4]<1 month in a 12-month period
Diagnosis	**Episodic tension-type headache**	**Chronic tension-type headache [5]**	**Episodic migraine (with or without aura)**	**Chronic migraine [6](with or without aura)**	**Episodic cluster headache**	**Chronic cluster headache**

Table 3 A summary of visual disturbances that can occur with head and neck pain.

	Description of visual disturbance	Unilateral	Bilateral	Length of onset	Maximal time to recovery	Differential diagnosis
Amaurosis fugax	Black out of whole or half of visual field	✓	x	Minutes (typically to 10 minutes)	No more than 1 hour	Atrial fibrillation Carotid bruit Internal carotid artery dissection or aneurysm Giant Cell Arteritis Vertebral basilar insufficiency Bilateral optic nerve disease (rare)
Visual aura	Zig-zag, flashing, scintillating scotoma	x	✓	Occurs over minutes (typically up to 30 minutes)	No more than 1 hour	Migraine
Transient visual obscuration	Greying or blacking out of vision	✓	✓	minutes	Seconds	Papilloedema Optic nerve swelling from other causes Uhthoff phenomenon