Migraine

David W Dodick

Migraine is a chronic paroxysmal neurological disorder characterised by multiphase attacks of head pain and a myriad of neurological symptoms. The underlying genetic and biological underpinnings and neural networks involved are coming sharply into focus. This progress in the fundamental understanding of migraine has led to novel, mechanism-based and disease-specific therapeutics. In this Seminar, the clinical features and neurobiology of migraine are reviewed, evidence to support available treatment options is provided, and emerging drug, device, and biological therapies are discussed.

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Department of Neurology, Mayo Clinic, Phoenix, AZ, USA (Prof D W Dodick MD)

Correspondence to:
Prof David W Dodick, Department of Neurology, Mayo Clinic, Phoenix, AZ 85054, USA
dodick.david@mayo.edu

Introduction

Migraine is a chronic neurological disorder characterised by attacks of moderate or severe headache and reversible neurological and systemic symptoms. The most characteristic symptoms associated with migraine include photophobia, phonophobia, cutaneous allodynia, and gastrointestinal symptoms such as nausea and emesis.[1] Additionally, patients can have a variety of other neurological symptoms—eg, vertigo, dizziness, tinnitus, and cognitive impairment.

Migraine often begins with premonitory symptoms hours or days before the onset of pain.[2] The most common premonitory symptoms include fatigue, impaired concentration, and neck stiffness. However, other psychological (anxiety, depression, irritability), arousal (drowsiness), neurological (photophobia), and cranial parasympathetic symptoms (lacrimation), and general symptoms (eg, yawning, increased urination, nausea, diarrhoea, and food cravings) can occur before the onset of pain.[3] Identification of premonitory symptoms could enable behavioural and treatment approaches that could mitigate or prevent the headache phase of migraine.

The migraine headache is often reported by patients to be unilateral (60%), throbbing (50%), and aggravated by physical activity (90%) or head movement.[1] The headache can change sides during or between attacks. The pain intensity is at least moderate or severe during attacks in most patients. The median time to peak intensity is 1 h and median duration is 24 h.[4] The duration of a migraine headache can range from 4 to 72 h in adults and 2 to 48 h in children. The pain can involve any part of the head and often involves the posterior cervical and trapezius regions.[4] Approximately 75% of patients have neck pain that accompanies their migraine episodes.[5] Additional symptoms that are not uncommon during migraine attacks are sinus pain or pressure (in 40% of patients)[6,7] and cranial autonomic features (in 50% of patients).[8] Headache can occur at any time of the day or night, but often occurs more during sleep, upon awakening, or shortly after rising in the morning than at other times.[9,10] Because migraine pain can be bilateral, mild, non-throbbing, or associated with neck pain, the condition can be misdiagnosed as a tension-type headache, whereas the occurrence of facial pain or cranial autonomic features could lead to a misdiagnosis of so-called sinus headache.[6]

The numerous symptoms that can occur during migraine attacks reflect the complex pathophysiology and diffuse involvement of multiple neural networks and anatomical regions in the brain. Photophobia (94%), phonophobia (91%), and dizziness (72%) are often reported by patients, as are anorexia and nausea, both of which occur in over half of patients.[11] Approximately a third of patients have vomiting and 16% of patients have diarrhoea during attacks.[11] Approximately 70% of patients have non-aura visual symptoms and about a third have osmophobia or hyperosmia.[12,13] Vertigo can be present during attacks of migraine, or can constitute the defining symptom of vestibular migraine, or a prominent symptom of migraine with brainstem aura.[14] Over 70% of patients have cutaneous allodynia—the perception of pain when non-painful stimuli are applied to the skin.[15,16] The presence of allodynia can be both predictive of a suboptimal response to triptans and a risk factor for progression to chronic migraine.[17]

The postdromal phase is defined as from when the headache resolves, to when the individual feels completely back to baseline. This phase occurs in about 80% of individuals with migraine,[18] and usually lasts less than 12 h, but can persist for longer than 24 h in approximately 12% of patients.[18–20] The most common symptoms during this phase include asthenia, fatigue, somnolence, impaired concentration, photophobia, irritability, and nausea. Patients also report a low threshold for recurrent brief head pain with the Valsalva manoeuvre or head movement.

In about a third of people with migraine, reversible neurological symptoms (migraine aura) can occur

Search strategy and selection criteria

I searched the Cochrane Library, MEDLINE, and Embase for paper published between Dec 1, 1945, and Dec 1, 2017. I used the search term "migraine" with the terms "headache" or "aura". I largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. I also searched the reference lists of articles identified by this search and selected those I judged relevant. Review articles and book chapters are cited to provide readers with more details and references than can be provided in this Seminar as a result of space restrictions. The reference list was modified on the basis of comments from peer reviewers.

Panel 1: Migraine without aura—International Classification of Headache Disorders-3[1]

1 At least five attacks fulfilling criteria 2–4
2 Headache attacks lasting 4–72 h (untreated or successfully treated)
3 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 (eg, walking or climbing stairs)
4 During headache at least one of the following: nausea or vomiting, or both; or photophobia and phonophobia
5 Not attributed to another disorder—eg, meningitis or brain hemorrhage

before the onset, during, or in the absence of pain. Migraine with aura is characterised by visual, sensory, language, or disturbances associated with brainstem dysfunction that usually last between 5 and 60 min and occur before the headache.[1] In a rare subtype of migraine, known as hemiplegic migraine, motor deficits might occur. However, the neurological symptoms can persist for over 60 min in a substantial minority of patients, and can occur simultaneously with or following the onset of headache.[21,22] The variable timing of aura and headache symptoms has challenged not only clinical beliefs, but also the biological basis and sequence of physiological events underlying a migraine attack.

Visual aura occurs in over 90% of patients with aura, and occurs in a hemifield as unformed flashes of light (spark photopsia), partial loss of vision (scotoma), or fortification phenomena (teichopsia).[23] A variety of other visual symptoms that are not considered diagnostic of aura but can be described by patients include shimmering, undulations, or so-called heatwaves. Other complex disorders of visual perception, including metamorphopsia, micropsia, macropsia, and zoom or mosaic vision. Paraesthesias are the second most common aura symptom and usually occur in conjunction with a visual aura. The paraesthesias usually involve the hand and perioral (cheiro-oral) region, and the arm, tongue, and lips, and can become bilateral. The paraesthesias usually progress (or march) and jump from one body part to another and, like visual symptoms, often transition from a postive sensation (paraesthesias—eg, scintillations) to a negative sensation (numbness—eg, scotoma). Expressive language dysfunction, or aphasia, is the least common aura symptom. Symptoms that are thought to reflect brainstem dysfunction (although their origin is unclear) can occur—eg, vertigo, dysarthria, ataxia, diplopia, and bilateral paraesthesias. Although higher order cortical deficits (eg, apraxia and agnosia) are rare, they can occur during migraine attacks, which underscores the CNS origin of aura symptoms.[24]

Because of the reversible nature of neurological impairment from migraine, distinguishing between migraine aura and transient ischaemic attack can be challenging, particularly in older adults who might have vascular risk factors and experience aura without headache. The characteristic features of migraine aura, which reliably distinguish the phenomena from transient ischaemic attack, include the following factors: the bilateral nature of the visual or sensory symptoms; positive and negative visual phenomena occurring sequentially or simultaneously; development of symptoms over at least 5 min and movement across the visual field or across different parts of the body, or both; and the sequential appearance of aura symptoms (eg, visual then sensory), and their stereotyped and often recurrent nature.[25]

In addition to migraine with and without aura, the International Classification of Headache Disorders has established operational diagnostic criteria for numerous other subtypes of migraine.[1] Notably, no pain or migraine-associated symptom criterion are sufficient or necessary for the diagnosis of migraine without aura (panel 1). The condition of probable migraine, which does not have either the requisite number of pain or associated symptom features to be defined as migraine, is an under-recognised migraine subtype that is believed to share an underlying biology with migraine and is treated in a similar fashion.[26] Patients with probable migraine are most likely often misdiagnosed as having tension-type headache. The diagnostic requirement for migraine of at least five discrete attacks ensures that serious systemic and intracranial diseases that could present with similar headache features and their associated symptoms are not overlooked.

Although migraine is often described as a paroxysmal disorder with discrete attacks separated by pain-free and symptom-free intervals, a substantial number of individuals with migraine could have very frequent attacks and interictal symptoms in the absence of pain.[20,27] Persistent symptoms are more likely to occur in individuals with chronic migraine than in those who have episodic migraine. Chronic migraine is defined by the presence of headache on more than 15 days per month, and that at least 8 days meet diagnostic criteria for migraine with or without aura.

Epidemiology

Migraine is one of the most prevalent and disabling medical illnesses in the world. WHO ranks migraine as the third most prevalent medical condition and the second most disabling neurological disorder in the world.[28,29] The 1-year prevalence of migraine in the general population is 12%.[30] The annual and lifetime prevalence are 18% and 33% in women, respectively, and 6% and 13% in men. Migraine affects approximately 10% of school-aged children (5–18 years), and at prepubertal ages (<13 years) the rate of onset of migraine is slightly higher in boys than in girls.[31] Although, for half of patients with migraine onset occurs before age 20 years, onset can

occur at an early age—eg, infantile colic has emerged as perhaps the earliest manifestation of migraine.[32] Migraine is most prevalent between the ages of 25 and 55 years, and the prevalence rises through early adult life and then falls after midlife (ie, 55 years).

Migraine also has a substantial burden on the entire family unit. In a longitudinal internet-based population study,[33] over half of people with migraine reported reduced participation in family activities compared with non-migraine controls and that they would be better partners and parents without migraine, and a third reported being worried about long-term financial security because of migraine. The financial cost of migraine is also a societal concern, with annual costs estimated to be in excess of US$20 billion.

The annual incidence of chronic migraine among people with episodic migraine is 2·5–3·0%.[34–36] The population prevalence of chronic migraine is approximately 2%, whereas about 8% of the migraine population has chronic migraine. Several modifiable risk factors increase the risk of developing chronic migraine, including high baseline attack frequency (one per week), overuse of acute medications, caffeine consumption, snoring, obesity, and the inadequate acute treatment of migraine attacks.[35,37,38] Female sex, allodynia, head injury, low socioeconomic status, depression, anxiety, and comorbid pain disorders are also risk factors for chronic migraine. The recognition and management of these risk factors and identifying people who already have chronic migraine is important. Compared with patients who have episodic migraine, individuals with chronic migraine have a substantially reduced health-related quality of life and their condition has a substantially greater effect on daily activities, direct medical costs, and prevalence of medical comorbidities.[39] Chronic migraine is also associated with a greater use of health-care resources, including more frequent visits to primary-care physicians, specialists, and emergency departments than episodic migraine. Individuals with chronic migraine are also more frequently admitted to and treated in hospital and undergo more diagnostic tests than those with episodic migraine.[40]

Despite the availability of evidence-based guidelines intended to inform clinical decision making and the care of patients with migraine, the management of migraine for the population remains suboptimal. Among people with chronic migraine, only 41% consult a health-care provider about their condition, and only 25% of these people receive an accurate diagnosis.[41] Even among those who receive an accurate diagnosis, over half are not prescribed an acute or preventive treatment. The use of screening tools, such as Identify (ID)-Migraine and ID-Chronic Migraine (ID-CM),[42,43] and evidence-based guidelines for the acute and preventive treatment of migraine, should enhance the likelihood of patients receiving an accurate diagnosis and optimal treatment.[44–51]

The overuse of acute headache medications is common among individuals with migraine who have frequent attacks, and this overuse poses a unique treatment challenge for clinicians. The 1-year population prevalence of chronic headache and medication overuse is approximately 1–3%.[52–55] Approximately 50% of patients seen in headache specialty centres overuse medication, and at least 50% of people with chronic migraine in the general population overuse acute medications. The threshold number of days that defines medication overuse depends on the medication (ie, >10 days per month for opioids, butalbital-containing medications, triptans, ergots, and combination analgesics; >15 days for simple analgesics such as non-steroidal anti-inflammatory medications). The greatest risk of progressing from episodic migraine to chronic migraine is associated with opioids (odds ratio [OR] 1·4) and butalbital-containing medications (OR 1·7) and can occur with as few as five doses per month.[52] Individuals with chronic migraine who overuse medication have an even poorer quality of life, greater disability, and greater losses in productivity than people who have chronic migraine without medication overuse.

Pathophysiology and genetics

Premonitory phase

The premonitory phase is the earliest stage of a migraine attack and it starts in the CNS. In a PET study of triggered and spontaneous attacks,[56] the earliest stage of the premonitory phase showed activation in the posterior and lateral regions of the hypothalamus and adjacent midbrain ventral tegmentum. Activation of these regions and their central connections to the limbic system could explain why migraine is commonly triggered by alterations in homoeostasis (eg, changes in sleep–wake cycles, missed meals) and also some of the symptoms during the premonitory phase—eg, yawning, polyuria, food cravings, and mood changes. The periaqueductal grey and dorsal pons, in the region of the noradrenergic locus coeruleus and serotonergic dorsal raphe nucleus, also show selective activation during the premonitory phase.[57] These regions are key for modulating the intensity of sensory stimuli (eg, light, sound), cerebral blood flow, nociception, and the excitability of cortical and subcortical neurons and glial cells. Involvement of these regions could account for alterations in cerebral blood flow seen during migraine attacks (with and without aura), amplification of ambient sensory stimuli (light, sound, odour), alterations in cortical excitability, and facilitation or disinhibition of trigeminal nociception.

Aura

Cortical spreading depression (CSD) is thought to be the underlying physiological cause of the aura phase of migraine.[58] CSD is an extreme depolarisation of glial and neuronal cell membranes that results in disruption of ionic gradients, a rise in extracellular potassium concentrations, release of glutamate, and a transient increase followed by a decrease in cerebral blood flow.

The spread of a CSD wave across neural tissue occurs at a rate of 2–6 mm/min—similar to the progression of the fortification spectra and cerebral oligaemia seen on cerebral blood flow imaging during aura in human beings.[59] Massive unregulated release of glutamate is considered to have an important role in the pathogenesis of CSD. The release of glutamate is mediated by intracellular calcium influx that is regulated by voltage-gated calcium channels, whereas the transporter-mediated astrocytic uptake of synaptic calcium is driven by sodium gradients that are maintained by the activity of sodium–potassium-ATPase (Na^+–K^+-ATPase) pumps.

The evidence that a CSD-like event is involved in the pathophysiology of migraine visual aura is based on blood oxygen level-dependent MRI during visual aura in human studies[59] and the identification of mutations in genes responsible for familial hemiplegic migraine (FHM) that result in excessive glutamate neurotransmission, enhanced neuronal excitability, and reduced thresholds for CSD in transgenic animals.[60] Additionally, CSD activates the trigeminovascular system[61] and effective migraine-preventive medications raise CSD thresholds in animal models.[62] Additionally, tonabersat—an experimental drug that inhibits CSD in animal models—has been shown to have preventive efficacy for migraine with aura,[63] and single-pulse transcranial magnetic stimulation (sTMS), which blocks CSD in animals,[64] has been shown to be effective for the acute treatment of migraine with aura.[65] Finally, although their development has been hampered by adverse events, glutamate receptor antagonists showed preventive efficacy in proof-of-concept studies.[66]

FHM is a rare monogenic autosomal-dominant subtype of migraine.[67,68] Gain-of-function mutations of *CACNA1A* (FHM type 1), which encode for the α1 subunit of neuronal $Ca_v2·1$ calcium channels on excitatory glutamate containing neurons, and of *ATP1A2* (FHM type 2), which encode for the α2 subunit of Na^+–K^+-ATPase pumps located on astrocytes, leads to net excitatory neurotransmission as a result of unregulated release or reduced uptake of synaptic glutamate. Loss-of-function mutations in *SCNA1* (FHM type 3), which encode the pore-forming α1 subunit of neuronal $Na_v1·1$ sodium channels on inhibitory interneurons, result in unregulated firing of excitatory neurons.

FHM-related mutations have not been shown to be relevant in migraine with or without aura. However, increased CNS excitability in individuals with migraine has been shown from induced and event-related potential studies by use of visual, auditory, somatosensory, and olfactory stimuli, as well as nociceptive brainstem reflexes.[69–71] These studies have consistently shown that, by contrast with people without migraine, for whom repetitive stimulation results in attenuated responses (habituation), individuals with migraine show unchanged or even increased responses.[72] This absence of habituation is seen between attacks and normalises just before and during an attack.

Although the underlying basis for this increased cortical excitability is unclear, a genetic influence seems likely. Missense mutations in the gene encoding casein kinase Iδ (*CKIδ*, also known as *CSNK1D*) has been found to be responsible for familial advanced sleep phase and migraine in two families.[73] Transgenic mice with a *Ckiδ* missense mutation (*Ckiδ*-Thr44Ala) show a significant reduction in their threshold for and an increased number of CSD events in response to a provocative stimulus. Additionally, genome-wide association studies have identified one DNA variant in the *MTDH* gene for migraine with aura and six gene loci (*MEF2D*, *TGFBR2*, *PHACTR1*, *ASTN1*, *TRPM8*, and *LRP1*) for migraine without aura as migraine susceptibility genes.[74] These genes are involved in glutamatergic neurotransmission or neuronal and synapse development and could influence the enhanced cortical excitability that is characteristic of migraine. A meta-analysis of genome-wide association studies involved 59 674 affected individuals and 316 078 controls from 22 studies.[75] Overall, 44 independent single-nucleotide polymorphisms were found to be significantly associated with migraine risk. These single-nucleotide polymorphisms mapped to 38 distinct genomic loci and included 28 loci that had not been reported before, including the first to be identified on chromosome X. Five of the loci involve or are linked to ion channels that influence neuronal excitability. However, loci that showed enrichment for genes expressed in vascular and smooth muscle tissues were also identified, indicating that vascular homoeostasis could influence the expression of the disease and might be integral to the pathogenesis of migraine, at least in some subgroups with migraine.

Functional imaging studies have also provided objective evidence that the brain of an individual with migraine is hyper-responsive to sensory stimuli even in the interictal phase between attacks.[76,77] Stimulus-evoked activation patterns in the brains of individuals with migraine show stronger activation in pain-facilitating regions and hypoactivation in pain-inhibiting regions than the brains of individuals without migraine.[78,79] These findings could explain the high sensitivity of people with migraine to noxious stimuli between attacks and their propensity to develop central sensitisation and allodynia during attacks. Visual stimuli also result in greater activation in the primary visual cortex and other visual processing regions—eg, the lateral geniculate nucleus[80,81] and motion-responsive middle temporal cortex—for individuals with migraine than individuals without migraine. This increased activation is especially true in individuals with migraine with aura, and is congruent with their vulnerability to CSD and visual aura.

Whether the enhanced cortical responsiveness in migraine is due to enhanced excitability or impaired inhibition is a matter of debate. Electrophysiological evidence[82] suggests that the imbalance between excitatory and inhibitory networks is due to deficient activity

of thalamocortical networks between attacks, which is caused by functional disconnections between the thalamus and other subcortical areas. Specifically, dysfunctional thalamocortical networks could be a result of altered top-down cortical feedback to the thalamus or bottom-up input from brainstem monoaminergic nuclei. The locus coeruleus and dorsal raphe nucleus provide extensive monosynaptic and paracrine neurotransmission to the thalamus and cortex, and these brainstem nuclei show altered activity throughout all phases of the migraine attack, during the postdromal phase in episodic migraine, and during the interictal phase in chronic migraine.[83–86] If this system is particularly vulnerable, potential trigger factors such as stressful life events, visual stimuli, hormonal changes, hypoglycaemia, or sleep deprivation could cause an attack. Therefore, abnormal modulation of excitability, rather than general hyperexcitability or hypoexcitability, could be the crucial underlying factor responsible for migraine attacks.

Headache phase

The headache phase of migraine is due to activation of trigeminal sensory pathways that innervate pain-sensitive intracranial structures, including the eye, dura mater, large cerebral and pial blood vessels, and the dural venous sinuses.[87] These structures are supplied by a plexus of largely unmyelinated fibres that project from the ophthalmic division of the trigeminal nerve and the upper cervical spinal roots. These peripheral trigeminal sensory afferents converge and synapse on second-order neurons in the trigeminal cervical complex.[88] This central convergence explains the characteristic distribution of migraine pain that includes the eye and periorbital region, the frontal and temporal head regions, and the referral of pain to the occipital nuchal regions. The second-order neurons within the trigeminal cervical complex project to the brainstem and hypothalamic, subcortical (basal ganglia), thalamic, and cortical regions that process nociceptive signals from the trigeminovascular system. Auditory, visual, and olfactory cortical areas that receive trigeminal sensory input could underlie the characteristic symptoms of migraine, whereas somatosensory, insular, retrosplenial, and parietal association cortical areas provide the sensory-discriminative, emotional, and cognitive appraisal of trigeminal nociceptive input.[89]

Trigeminal sensory fibres that innervate the meninges also project branches that cross the calvarial sutures and supply the periosteum and pericranial muscles.[90] Extracranial activation of meningeal nociceptors by extracranial causes (eg, head trauma, pericranial muscle inflammation), or activation of extracranial sensory fibres via activated meningeal nociceptors, provide mechanisms by which extracranial pathology can trigger migraine attacks in susceptible individuals, and pericranial muscle tenderness can result from a migraine attack triggered by an intracranial process.[91]

Sensory transmission of nociceptive signals from peripheral trigeminal sensory afferents to second-order neurons involves the release of several neurotransmitters, including calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38), glutamate, and nitric oxide.[92] Release of CGRP and PACAP-38 also results in cranial vessel dilation and mast-cell degranulation, both of which could further activate vascular and meningeal nociceptors and contribute to migraine headache. Activated meningeal nociceptors could become sensitised (response threshold decreases and response magnitude increases) leading to a nociceptive response to stimuli that normally would not cause pain (eg, pulsation of blood vessels, increased CSF pressure associated with the Valsalva manoeuvre). The sensitisation of peripheral trigeminal sensory afferents could also lead to sensitisation of second-order and third-order neurons in the trigeminal cervical complex and sensory thalamus,[61] which could account for cephalic (scalp sensitivity and muscle tenderness) and extracephalic (skin sensitivity in limbs or aching muscles) allodynia that occurs in most individuals during migraine attacks. Central sensitisation is present between full-blown migraine attacks in people with chronic migraine and could account for the low-grade headache, allodynia, and other symptoms that are characteristic of this disorder. Sensitisation of third-order thalamic neurons also appear to underlie some of the associated symptoms of migraine—eg, photophobia. Intrinsically photosensitive retinal ganglion cells in the retina have been found to project to dural-sensitive thalamic neurons in the posterior thalamus.[93] The activity of these neurons, especially when sensitised, is significantly enhanced and their projection to multiple cortical areas, including the somatosensory and visual cortices, explains in part why light exacerbates head pain during a migraine attack. Repeated attacks of central sensitisation along with dysfunctional descending pain modulation could result in the progression and persistence of symptoms and the development of chronic migraine. The attack-related electrophysiological changes and increase in serum CGRP concentration seem to persist in the interictal phase in individuals with chronic migraine.[94] A state of sustained central sensitisation can result in amplification of subthreshold events (migraine triggers) resulting in frequent migraine attacks. Such neural plasticity can be viewed as a type of so-called pain memory and is evident in functional MRI studies that show increased functional connectivity in the resting state within the matrix of networks that facilitate pain as the attack frequency increases.[76] The induction of latent trigeminal sensitisation by drugs promoting medication-overuse headache also produce analogous neural adaptations that promote enhanced susceptibility to subthreshold triggers mediated through descending pain-modulatory circuits.[95] This latent sensitisation has been shown in animal models after persistent exposure to opiods or triptans and is

	Half-life (h)	Dose (mg)	Number needed to treat (2 h pain relief)
Aspirin			
Tablet, intravenous, or combined with caffeine and paracetamol	0·25	975–1000	4·9
Salicylate (active form)	5–6 (after 1 g dose)	975–1000	3·3*
Ibuprofen			
Tablet	2	400	3·2
Naproxen			
Tablet	14	500–550 (up to 825 mg)	7·0
Diclofenac potassium			
Tablet	2	50	6·2
Powder for oral solution	2	50	4·5

Elimination is given as half-life. *With metoclopramide.

Table 1: **Simple analgesics used by individuals with migraine**

associated with increased expression of CGRP and neuronal nitric oxide synthase in trigeminal ganglia neurons that persist long after discontinuation of either opiate or triptan exposure.[96] These changes are blocked by the co-administration of inhibitors of neuronal nitric oxide synthase and anti-CGRP monoclonal antibodies and suggest a potential role for such compounds for the treatment of medication-overuse headache.[97] Triptan exposure has also been shown to reduce the stimulation threshold to result in a CSD event, and this event was blocked by topiramate.[98] Taken together, these studies provide evidence that chronic migraine and medication-overuse headache might be associated with enhanced cortical excitability and dysfunction of endogenous pain modulatory systems, leading to the development of persistent central sensitisation.

Acute treatment

Acute treatment of migraine includes the use of drug therapy and behavioural techniques. Several general principles improve outcomes for acute treatment, including giving acute medication early while pain is mild, and choosing the right dose and route of administration. A non-oral route of administration (eg, nasal spray, injection, suppository) can improve patient outcomes in those who typically are awakened by moderate-to-severe attacks, or whose pain peaks rapidly (ie, within 30 min), and could also be advisable for those with nausea or vomiting during the premonitory period or early in the course of the attack.[99] A combination of acute medications that possess different mechanisms of action could also be of use for patients who do not achieve rapid relief or who have recurrent headache within 24–48 h after initial relief.[100] The education of patients with frequent migraine attacks about the potential for medication-overuse headache is important, and minimising the use of simple analgesics (eg, non-steroidal anti-inflammatory drugs, paracetamol) to less than 15 days per month, and triptans, ergots, or combination analgesics to less than 10 days per month.[1,53]

Simple analgesics are used by most individuals with migraine and have been shown to be effective for mild or moderate pain (table 1). Additionally, although stratified care (ie, matching attack severity to treatment intensity) has been shown to improve outcomes for acute treatment, some patients can use a step-care within attack strategy by first using simple analgesics and only stepping up to a migraine-specific medication if the pain progresses.[101]

When contraindications do not exist, triptans are widely considered to be first-line drugs for patients with migraine attacks associated with moderate or severe pain intensity.[44,48] Triptans are highly selective serotonin 5-HT_{1B} and 5-HT_{1D} receptor agonists, and some have activity at the 5-HT_{1F} receptor as well. These receptors are located on peripheral trigeminal sensory nerve endings and on neurons in the trigeminal cervical complex, rostral brainstem, and thalamus. Triptans also bind to 5-HT_{1B} receptors located on intracranial, extracranial, and systemic blood vessels and can cause vasoconstriction. Overall, based on extensive clinical trial experience and over 25 years of use in clinical practice, the incidence of adverse vascular events is rare when triptans are used appropriately and according to prescribing guidelines.[102] However, when the vascular safety profile of triptans was analysed by the US Food and Drug Administration (FDA) Adverse Event Reporting System database, with a focus on serious and unexpected adverse events, unexpected associations were revealed between triptan use and ischaemic cerebrovascular events, aneurysms and artery dissections, and pregnancy-related vascular events. These associations underscore the rationale for the contraindication of triptans in patients with a history of symptomatic peripheral, coronary, and cerebrovascular disease and severe hypertension, and the caution that is taken in prescribing them to patients with vascular risk factors. In the absence of vascular risk factors and contraindications, triptans have shown an overall favourable safety profile and in some European countries they are available without a prescription.

Triptans are available in a variety of formulations (table 2). This variety allows the patient and clinician the ability to individualise the mode of administration on the basis of different attack profiles between patients and within the same patient. For triptans with multiple formulations, patients have the flexibility to establish which formulation is most appropriate for a given attack. For example, an attack that begins during waking hours and progresses slowly might be treated with an oral tablet, but an attack that awakens a patient from sleep and is already severe might be better treated with a non-oral formulation.

Despite the similar target specificity of all triptans, the efficacy and side-effect profiles can differ substantially from patient to patient. To achieve a pain-free state at 2 h, subcutaneous sumatriptan has the lowest number needed to treat (table 2);[48,103] however, most patients prefer oral triptans. Selection of formulation should be on the

basis of a combination of the best evidence, patient preference and sensitivity to side-effects, and the characteristics of individual attacks (eg, time to peak intensity, propensity for recurrence). Pain-free rates at 2 h are highest for eletriptan 40 mg and rizatriptan 10 mg. Eletriptan 40 mg and frovatriptan 2·5 mg are associated with the lowest recurrence rates, whereas almotriptan 12·5 mg and naratriptan 2·5 mg are associated with a low incidence of side-effects.[100,103] Rizatriptan, frovatriptan, and zolmitriptan might be preferred in patients with a severe allergy to sulphonamide, because they do not have a sulpha moiety.

Dihydroergotamine can be self-administered by nasal spray, or subcutaneous or intramuscular injection, and can be of use in patients who do not respond to or tolerate triptans. Dihydroergotamine appears to be effective in reversing central sensitisation, which could explain why it does not appear to induce medication-overuse headache, its clinical utility in reducing headache recurrence, and its use as an acute medication option for those withdrawing from overuse of triptans or analgesics.[104,105] Oral ergotamine tartrate is seldom given to patients because of its poor oral bioavailability, lower efficacy than triptans, and its association with frequent occurrences of nausea. Little evidence exists for the use of oral or parenteral opioids or butalbital-containing analgesics for the acute treatment of migraine, and all evidence-based guidelines recommend against their routine use because of the high incidence of adverse events and the risk of habituation, addiction, tolerance, withdrawal syndromes, and medication-overuse headache.[44,48,106]

	Route	Number needed to treat (2 h pain free)
Sumatriptan 6 mg	Subcutaneous	2·3
Sumatriptan 20 mg	Intranasal	4·7
Zolmitriptan 5 mg	Intranasal	4·6
Almotriptan 12·5 mg	Oral	4·3
Eletriptan 20 mg	Oral	10
Eletriptan 40 mg	Oral	4·5
Frovatriptan 2·5 mg	Oral	8·5
Naratriptan 2·5 mg	Oral	8·2
Rizatriptan 10 mg	Oral	3·1
Sumatriptan 50 mg	Oral	6·1
Sumatriptan 100 mg	Oral	4·7
Zolmitriptan 2·5 mg	Oral	5·9

Migraine attacks were treated at moderate or severe intensity. Numbers needed to treat might be lower than indicated in the table when treatment is administered early while pain is mild.

Table 2: **Triptans—route and efficacy based on the number needed to treat[100]**

Panel 2: **Preventive medications—general principles of use for prescribing health-care providers**

- Begin with the lowest possible dose and increase it slowly; stop dose escalation when adverse events occur, or when efficacy or target dose achieved
- Consider comorbid (eg, depression, epilepsy) and coexistent illnesses (eg, hypertension, obesity) when selecting drug, but recognise that monotherapy might not be optimal for treating two disorders (eg, a small dose of tricyclic antidepressant for the treatment of both migraine and depression)
- A 2–3 month trial is necessary to determine efficacy; a 6-month trial might be necessary before the maximal response is evident
- Target goals: reduction in frequency, severity, or duration of acute attacks, or a combination of these
- Discuss family planning and potential adverse fetal effects of antimigraine medications with all potentially childbearing female patients
- Discuss potential adverse drug-related events with patients; some might be self-limited and dose dependent

Preventive treatment

Preventive medications are of use to reduce the frequency, severity, and duration of attacks in people with frequent migraine. Since attack frequency is a risk factor for progression to chronic migraine, preventive medications should be given when migraine attacks are frequent (ie, four or more attacks per month, or ≥8 headache days per month).[107] Such medications should also be considered for individuals whose attacks substantially interfere with their quality of life despite appropriate use of acute medications and lifestyle modification strategies, or if contraindications, treatment resistance, or adverse events preclude the use of effective acute medications. Preventive medications might also be preferred by patients with a low frequency of attacks and they should be considered, regardless of attack frequency, for patients with the following rare migraine subtypes: hemiplegic migraine; migraine with brainstem aura; frequent, prolonged, or uncomfortable aura symptoms; or migrainous infarction.

The adherence to preventive medications is poor even among individuals with chronic migraine.[108] Therefore, physician adherence to specific guiding principles could enhance patient compliance and outcomes (panel 2).[109] Special care, counselling, and education should be exercised when prescribing preventive medications for women of childbearing age because of the potential for toxic effects in fetuses and teratogenicity associated with some of the more common preventive medications.

The medications used for migraine prevention, their evidence base, and their dose ranges are given in table 3. In an evidence-based guideline from the Canadian Headache Society[46] that incorporated clinical experience and the propensity for adverse events into the strength of recommendation, the following drugs and agents received strong recommendations for use: topiramate, propranolol, nadolol, metoprolol, amitriptyline, gabapentin, candesartan, riboflavin, ubidecarenone (coenzyme Q10), and magnesium citrate. However, in other guidelines that are based on published studies,[51] the evidence supporting the efficacy of gabapentin is

	Level of evidence	Daily dose
β blockers		
Atenolol	B	50–200 mg once a day
Metoprolol	A	50–200 mg once a day for long-acting formulation
Nadolol	B	20–160 mg once a day
Propranolol	A	40–240 mg once a day for long-acting formulation
Antidepressants		
Timolol	A	20–60 mg once a day
Amitriptyline	B	10–50 mg before bed
Nortriptyline	..*	10–150 mg before bed
Venlafaxine	B	75–225 mg once a day for long-acting formulation
Calcium-channel blockers and anticonvulsants		
Verapamil	U	120–960 mg in divided doses for long-acting formulation
Flunarizine	A	5–10 mg once a day
Gabapentin	U	600–3600 mg in two–three divided doses
Topiramate†	A	50–200 mg twice a day or before bed
Valproic acid–divalproex†	A	500–2000 mg once a day or in two divided doses
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers		
Lisinopril	C	10–40 mg once a day
Candesartan†	C	16–32 mg once a day
Cyproheptadine	C	4–16 mg before bed
Ibuprofen	B	200 mg twice a day
Fenoprofen	B	200–600 mg twice a day
Ketoprofen	B	50 mg three times a day
Naproxen	B	500–1100 mg once a day
Naproxen sodium	B	550 mg twice a day
Miscellaneous agents		
Feverfew	B	50–82 mg once a day
Riboflavin	B	400 mg once a day or 200 mg twice a day
Ubidecarenone (coenzyme Q10)	C	300 mg once a day
Magnesium citrate	B	400–600 mg once a day
OnabotulinumtoxinA‡	A	155–195 mg once every 12 weeks (for chronic migraine)

Data are from Canadian Headache Society guidelines[46] and Holland et al.[51] Levels of evidence to support use as preventive medication are defined as follows: level A: drug has been established as effective (requires at least two consistent class 1 studies); level B: drug is probably effective (requires at least one class 1 study or two consistent class 2 studies); level C: drug is possibly effective (requires at least one class 2 study or two consistent class 3 studies); level U: data are inadequate or conflicting, treatment is unproven. *Used in clinical practice but no level of evidence since no studies have been done. †For pregnant women, drugs are reclassified as FDA Pregnancy category D because of the risk of fetal malformation. ‡Approved for the preventive treatment of chronic migraine, not episodic migraine FDA=US Food and Drug Administration.

Table 3: **Preventive medications for migraine**

inadequate or conflicting (ie, level U) and only supports a recommendation of possibly effective (level C) for candesartan and lisinopril (for description of evidence levels see table 3).

In addition to avoidance of reproducible and predictable trigger factors, behavioural treatments, including biofeedback-assisted relaxation training and cognitive behavioural therapy, have been shown to have an efficacy similar to preventive drugs. Therefore, such treatments could be useful for patients with migraine who cannot take preventive medications because of contraindications, or a history of poor response or adverse effects.[47,110–113] Behavioural treatments should also be considered for women who are pregnant or lactating, individuals with medication-overuse headache, and those who express a preference for non-drug treatments, identify life stress as a trigger factor, or have poor coping skills or comorbid psychological disorders that might amplify the disability associated with migraine attacks. In addition to behavioural techniques, aerobic exercise could reduce attack frequency and improve patient outcomes to a similar degree as preventive medications.[114]

The evidence base for the management of chronic migraine is less robust than that of episodic migraine. Preventive medications should be considered in most patients with chronic migraine. OnabotulinumtoxinA and topiramate have been shown to be effective for individuals with chronic migraine, even when acute medications are overused.[53,115–117] The evidence is strongest for onabotulinumtoxinA and, according to a guideline from the American Academy of Neurology,[118] should be offered as preventive medication for individuals with chronic migraine.

The optimal management approach to patients with chronic migraine who also overuse acute medications is a unique challenge for clinicians since the best treatment strategy is uncertain. A guideline for the treatment of medication overuse published by the European Federation of Neurological Societies concluded that "only a few controlled and/or randomized trials are available to give evidence-based recommendations for the treatment of [medication-overuse headache]".[119] The consumption of acute medications should be reduced and restrictions on the number of days of use per week should be imposed to reduce headache frequency and minimise the risk of systemic, renal, gastrointestinal, and cardiovascular toxic effects. However, debate and clinical equipoise continue regarding the best strategy to discontinue the medications that are being overused, acutely manage the inevitable withdrawal headaches and recurrent migraine attacks, and whether to initiate preventive medication at the same time as withdrawal is initiated.[120]

A systematic review has shown a low level of evidence to support discontinuation of overused medications without initiating preventive medication.[120] Adding preventive medication to acute drug discontinuation led to better outcomes than discontinuation alone, and some evidence suggests that preventive medication alone could be superior to drug discontinuation alone. However, randomised controlled trials are needed to assess the safety and long-term efficacy of preventive medication plus discontinuation versus preventive medication alone versus discontinuation alone. A large pragmatic multicentre trial is assessing abrupt discontinuation plus prevention versus prevention alone (NCT02764320).

Emerging treatments

The presence of serotonin 5-HT_{1B} receptors on blood vessels and the cardiovascular liability associated with

targeting this receptor has prompted the development of lasmiditan, a 5-HT_{1F} receptor agonist that does not have activity at the 5-HT_{1B} receptor, therefore making it more selective than available serotonin receptor agonists and removing any vasoconstricting effect. Lasmiditan is a highly selective 5-HT_{1F} receptor agonist that has been shown in randomised, double-blind, placebo-controlled studies to be effective for the acute treatment of migraine.[121] The most common adverse events were vertigo and dizziness, which could be due to activation of 5-HT_{1F} receptors in the lateral vestibular nucleus, temporoparietal cortex, or cerebellum, or a combination of these. Two large, phase 3 placebo-controlled trials have been completed for this drug (NCT02439320, NCT04239320). Although the full results of these trials have not yet been peer reviewed and published, on the basis of abstract presentations from the study investigators at the International Headache Congress in Vancouver, BC, Canada, in September, 2017,[122] the trials seem to have confirmed the efficacy and safety of lasmiditan. The preliminary efficacy seen with lasmiditan shows the potential for drugs that do not have vasoconstrictor activity to be effective and acute antimigraine drugs.

On the basis of the abundance of evidence for the integral role of CGRP in the pathophysiology of migraine, six small-molecule CGRP receptor antagonists (gepants) have been developed and shown to be effective for the acute treatment of migraine.[123–127] The development of two of these drugs (telcagepant and MK-3207) was terminated because of liver toxicity, but several others are in development. Overall, these studies confirm that CGRP receptor antagonists are effective acute-migraine therapies and, like lasmiditan, do not have vasoconstrictor activity and are a promising therapeutic target.[128]

The pivotal role of CGRP in the pathogenesis of migraine also prompted the development of monoclonal antibodies targeting either GCRP or its receptor. Subcutaneously administered anti-CGRP monoclonal antibodies targeting the peptide (fremanezumab, galcanezumab) or its receptor (erenumab) have now been shown in pivotal trials to be well tolerated and efficacious for the prevention of episodic migraine and chronic migraine.[129–137] Eptinezumab, an intravenously administered anti-CGRP monoclonal antibody, has also been reported to be effective for the preventive treatment of episodic migraine in a phase 2 randomised placebo-controlled trial, and of chronic migraine in a phase 3 placebo-controlled trial.[131,138] The positive results of a phase 3 trial of eptinezumab for the preventive treatment of chronic migraine were also announced but are as yet unpublished. Trials for galcanezumab and fremanezumab for the preventive treatment of episodic and chronic cluster headache are ongoing. These protein antibodies should not have off-target toxic effects since they are catabolised into their own constitutive aminoacids.

The long half-life (3–6 weeks) of these monoclonal antibodies should enable monthly (erenumab, galcanezumab, fremanezumab) subcutaneous dosing, or a single subcutaneous (fremanezumab) or intravenous (eptinezumab) dose with a 3-month evaluation of efficacy. The vascular safety of sequestering or blocking the receptor of a potent vasodilator, CGRP, especially during times of acute vascular stress (eg, stroke, myocardial infarction, hypertension) could be a concern.[139] A 2017 study (abstract presentation at the 2017 International Headache Congres[140]) assessing the cardiovascular safety of individuals with stable angina showed no difference in ST-segment depression, or time to total treadmill exercise time or onset of exercise-induced angina in patients given erenumab 140 mg intravenously compared with placebo. However, the safety of CGRP monoclonal antibodies in clinical situations in which the blood–brain barrier is disrupted (eg, meningitis, head trauma) is unclear. Additionally, given the long biological half-life of the antibodies, their ability to cross the placental barrier, and the predominance of migraine in women of childbearing age, their effect on a developing fetus and safety during pregnancy need to be clarified. Most available therapeutic monoclonal antibodies for the treatment of inflammatory and autoimmune diseases carry an FDA pregnancy rating of category B or C. During the first 20–22 weeks of pregnancy, minimal active transfer occurs for most monoclonal antibodies because of the absence of the neonatal Fc receptor, which transports high molecular weight immunoglobulin G (Ig) antibodies across the placenta.[141–143] However, transfer of IgG antibodies progressively increases over the course of a pregnancy as neonatal Fc receptors are expressed, and CGRP might have a role in the regulation of uteroplacental blood flow during pregnancy.[144] Long-term open-label extension studies and post-marketing data should provide additional safety data on these new biologics.

Several neuromodulation devices have emerged as being effective for acute or preventive migraine treatment. In a randomised, double-blind, parallel-group, multicentre, phase 2 sham-controlled study,[65] sTMS was shown to be effective for the acute treatment of migraine with aura. The incidence and severity of adverse events were similar between the sTMS and sham groups. sTMS was approved by the FDA for the acute treatment of migraine with aura in 2014. On the basis of a prospective open-label observational trial in which patients delivered four pulses twice daily, sTMS was FDA approved for the acute and prophylactic treatment of migraine headache.[145]

The preventive efficacy of an external trigeminal nerve stimulation for migraine was assessed in a double-blinded, randomised, sham-controlled trial involving 67 patients with episodic migraine who applied the device for 20 min per day over a 3-month period.[146] The proportion of patients who had a greater than 50% reduction in mean monthly migraine days was

significantly greater in the active group than the sham group (38·1% *vs* 12·1%; p=0·023). However, the other primary endpoint of a reduction in mean monthly migraine attacks between baseline and the third month of treatment was not significantly different between the two groups (6·94 to 4·88 in the active group *vs* 6·54 to 6·22 in the sham group; p=0·054). The device received regulatory approval in the USA and some European countries for preventive treatment of episodic migraine, and on Sept 15, 2017, on the basis of a sham-controlled trial presented at the International Headache Congress as a late-breaking abstract,[147] was approved by the FDA for the acute treatment of migraine with or without aura.

Non-invasive vagus nerve stimulation (nVNS) has been assessed for the acute and preventive treatment of migraine and cluster headache. Despite open-label evidence of efficacy, nVNS did not significantly reduce migraine frequency in a small, randomised, sham-controlled study in people with chronic migraine.[148] nVNS has been assessed for the acute and preventive treatment of episodic migraine in two large sham-controlled trials (NCT02378844, NCT02686034). In a study assessing the efficacy of nVNS for the acute treatment of migraine,[149] nVNS treatment did not achieve statistical significance for the primary endpoint of a pain-free state at 2 h (30·4% *vs* 19·7%; p=0·067). However, significantly higher pain-free rates compared with sham groups were achieved at 30 min (12·7% *vs* 4·2%; p=0·012) and 60 min (21·0% *vs* 10·0%; p=0·023). In January, 2018, nVNS was approved by the FDA for the acute treatment of migraine pain. It has also shown preliminary efficacy for the preventive treatment of cluster headache[150] and has been shown to be effective for the acute treatment of cluster headache attacks in patients with episodic cluster headache, and has received approval for this indication.[151,152]

In 2017, the efficacy of remote, non-painful, electrical upper-arm skin stimulation was assessed in a placebo-controlled trial for the acute treatment of migraine.[153] Electrodes were applied to the skin of the upper arm for 20 min after the migraine attack began. A positive headache response at 2 h was seen in 58% of patients in the active treatment group versus 24% in the placebo group (p=0·02). Pain-free responses at 2 h were seen in 30% of the treated patients compared with 6% of the placebo group (p=0·004). The rationale of remote electrical stimulation is based on the activation of descending inhibition pathways via a conditioned pain-modulation effect.[154]

Infiltration of local anaesthetic (with or without corticosteroid) around extracranial nerves, especially the greater occipital nerve, has long been of use for the acute and preventive treatment of migraine and a variety of other headache disorders. However, no placebo-controlled evidence seems to support the use of an extracranial nerve blockade for the acute treatment of migraine. Although the data on the preventive efficacy of greater occipital nerve blockades is mixed,[155] a meta-analysis of six randomised trials showed that, compared with control interventions, a greater occipital nerve block can reduce the number of headache days and medication consumption of patients with migraine.[156]

A supportive consensus statement from the American Headache Society[157] outlined the procedural aspects that should be used in clinical practice when administering both extracranial nerve blocks and trigger point injections. The nerves targeted include the supraorbital, supratrochlear, greater and lesser occipital, and auriculotemporal nerves, and the sphenopalatine ganglion.

Prognosis

The long-term prognosis of migraine varies considerably between individuals. Outcomes range from complete or partial clinical remission, to decades of attacks that do not change in frequency, severity, or symptom profile (ie, persistence), or to the development of chronic migraine (ie, progression). The management of risk factors for chronic migraine is sound and appropriate, although management of risk factors has not yet been shown to influence progression. Untreated chronic migraine can remit to an episodic pattern. Headache frequency (15–19 *vs* 25–31 headache days per month) and the absence of allodynia are two factors that increase the probability of conversion of chronic migraine to episodic migraine.[158,159]

Structural brain changes occur over time in individuals with migraine. A population-based study in the Netherlands showed that hyperintense lesions in the brain white matter accumulated over a 9-year period in female patients with migraine.[160] The increase in lesions did not affect cognition and no relationship was found between frequency or subtype of migraine and lesion progression.

Evidence is increasing for other functional and structural brain changes that appear to occur with increasing migraine frequency. Key structural differences in cortical thickness in the somatosensory cortex and insula were found in individuals with high migraine attack frequency, indicating the potential for repeated sensory activation during attacks to lead to adaptive changes in regions of the brain that process sensory information and modulate the affective response to pain.[161] Additionally, as migraine frequency increases, stronger activation is seen in regions that facilitate pain and weaker activation is seen in regions that inhibit pain.[79] In a 2015 study,[162] brain cortical thickness, cortical surface area, and regional volumes were highly accurate in distinguishing individuals with chronic migraine from those with episodic migraine and non-affected controls. Moreover, individuals with migraine have age-related thinning of specific brain regions, suggesting that the migraine disease process interacts with ageing to affect cortical integrity.[163] The extent to which these changes have neurological consequences or are modifiable with effective treatment is unknown.

Controversies and uncertainties

A fundamental question in migraine pathogenesis is whether, and by what mechanisms, the trigeminovascular system becomes activated as a result of central changes that occur during the premonitory or aura phase. In migraine with aura, the prevailing hypothesis is that CSD is a noxious event that leads to activation of meningeal nociceptors. In a rodent-model studies,[164] CSD induces a significant but delayed (14–25 min) increase in the firing of meningeal nociceptors. The delay seen between the wave of CSD and activation of the trigeminovascular fibres correlates with the delay often seen between the onset of aura and the beginning of the headache. CSD might activate meningeal nociceptors by inducing an inflammatory cascade through the activation and opening of pannexin-1 megachannels.[165] Pannexin-1 activation leads to the release of proinflammatory mediators such as high mobility group B1 (HMGB1) from neurons, which initiates a parenchymal inflammatory response that leads to sustained release of inflammatory mediators and prolonged trigeminal stimulation. The time required for the transduction of this inflammatory cascade could explain the delay between CSD and the activation of nociceptors.

CSD could also activate second-order neurons within the trigeminal cervical complex directly.[166] Descending cortical projections from somatotopically specified insular and primary somatosensory cortices terminate in contralateral laminae I–II and III–V of the trigeminal cervical complex. These projections might provide top-down control of trigeminal nociception and explain how selective facilitation or disinhibition of second-order neurons within the trigeminal cervical complex lead specifically to cephalic pain. Animal studies[166] have shown that CSD leads to a significant increase in the firing of second-order trigeminovascular neurons in the trigeminal cervical complex, even after peripheral trigeminal nociceptors are blocked by lidocaine injections into the trigeminal ganglion. The mechanism by which this process occurs is unclear, but that CSD can disrupt the ability of the dorsal raphe nucleus to inhibit trigeminovascular nociception suggests that descending inhibition of nociceptive traffic from the trigeminal cervical complex is impaired.

In migraine without aura, the mechanism through which peripheral or central trigeminovascular nociception, or both, occur is uncertain. One speculation is that CSD might occur in individuals who have migraine without aura but remain clinically silent or give rise to atypical aura symptoms.[167] Although the evidence of this proposed mechanism is sparse, CSD is known to occur in cortical regions other than the visual or somatosensory cortex and in subcortical tissues, including the striatum, hippocampus, and thalamus.[168] Additionally, support for this hypothesis comes from a PET study[167] of an individual with migraine without aura who was participating in a visual-activation paradigm. The patient developed a migraine attack without typical aura (visual blurring) and a bilateral decrease in cerebral blood flow—beginning in the visual-association cortex and spreading to the occipitotemporal and parietal cortex—occurred at a rate of 2–6 mm/min.

An alternative hypothesis accounting for headache in migraine without aura is via descending facilitation or impaired descending inhibition of central trigeminovascular neurons. Functional imaging studies have shown early activation in the hypothalamus, midbrain, and dorsal rostral pons.[56,86,169,170] Hypothalamic neurons that respond to changes in physiological and emotional homoeostasis can activate meningeal nociceptors by enhancing parasympathetic tone and the release of vasoactive intestinal polypeptides.[171,172] Hypothalamic and brainstem neurons can reduce the threshold for transmission of nociceptive trigeminovascular signals from the thalamus to the cortex.[173] These regions also provide descending input that both facilitates and inhibits neurons within the trigeminal cervical complex via the rostral ventromedial medulla and other brainstem nuclei including the dorsal raphe nucleus, locus coeruleus, and nucleus cuneiformis. Persistent activation of midbrain and dorsal pontine structures in the headache phase and the pain-free state after treatment, and hypoactivation of the nucleus cuneiformis suggest the possibility of altered modulation of the trigeminal cervical complex neurons that are responsive to basal sensory afferent traffic from meningeal nociceptors.[83,84]

Additionally, controversy exists over whether activation of peripheral trigeminal nociceptors is necessary for the development of a migraine headache. Supporters of the peripheral theory maintain that, although the genesis of the attack might begin in the CNS, peripheral nociceptor activation, even from extracranial afferents, is a prerequisite for the generation of the headache phase of migraine.[174] Alternatively, the central theory proposes that central events (eg, CSD or altered descending modulation of nociceptive transmission) can enable and amplify basal sensory signalling from meningeal nociceptors and other sensory modalities (eg, light, sound, touch, smell) without altering the peripheral sensory environment.[92] It is possible, and probable, that these theories are not mutually exclusive and that migraine is a genetically predetermined permissive brain state with hyperexcitable central networks. In a cyclic manner, or within the context of endogenous or external trigger factors, these networks amplify basal sensory afferent traffic or is hyperresponsive to peripheral stimuli that increase nociceptive traffic along peripheral trigeminal or cervical sensory afferents (eg, head trauma, whiplash, sinus mucosal inflammation, blunt head trauma).

As an extension of this argument, an unresolved question is whether acute and preventive drugs can stop or prevent attacks through a purely peripheral mechanism, or whether penetration of the blood–brain

barrier is necessary to gain access to central targets involved in stopping the attack. No conclusive evidence that the blood–brain barrier is breached either during or between attacks seems to exist. In fact, evidence suggests that the blood–brain barrier is intact even during attacks.[175] Triptans are largely hydrophilic drugs that were designed to bind to peripheral serotonin receptors located on intracranial blood vessels and were later found to be agonists at receptors located on trigeminal nerve terminals. As such, these drugs were thought to exert their therapeutic effect outside the blood–brain barrier by reducing sensory transmission from the first-order to the second-order neurons. However, central side-effects (eg, sedation) do occur, their receptor targets are located on second-order and third-order trigeminovascular neurons, and application of triptans in animal models at central sites can potently modulate ascending nociceptive traffic from the trigeminal cervical complex.[176]

The evidence that anti-CGRP monoclonal antibodies[129–135] are effective for the prevention of migraine supports a peripheral mode of action. These are large molecules that do not penetrate the blood–brain barrier in quantities that are likely to be sufficient for them to have a central mechanism of action. In experimental animal models, fremanezumab, a humanised CGRP monoclonal antibody, was shown to prevent CSD-induced activation and sensitisation of high-threshold trigeminovascular neurons and the activation of Aδ-type but not C-type meningeal nociceptors.[177,178] These data support that this antimigraine drug was the first that seemed to be selective for peripheral Aδ-fibres and central high-threshold neurons, and, according to the authors, suggest that the initiation of the headache phase of migraine depends on activation of meningeal nociceptors, and that for some patients activation of the Aδ-high-threshold pain pathway might be sufficient for the generation of headache perception. Considering these data, interrupting the afferent traffic along peripheral sensory fibres could modulate central networks that are responsible for generating a migraine attack. Therefore, migraine attacks could be stopped and prevented by decreasing either peripheral trigeminovascular sensory transmissions or directly modulating central networks that control the ascending transmission of nociceptive signals from central trigeminovascular neurons.

Outstanding research questions

Several key questions will guide future efforts in migraine research. The molecular switch that stops an attack is still unknown. Similarly, from disease course and prognosis perspective, establishing the factors that influence remission and progression to persistent symptoms over time will be crucial in guiding the development of disease-modification strategies. Answers to these questions could produce a druggable target that prevents progression and prevents or terminates the attack.

The development of clinical, genetic, serum, or imaging biomarkers, or a combination of these, that predict treatment response and clinical disease course would begin an era of precision medicine for people with migraine. Pursuing established (eg, CGRP, PACAP-38) and uncovering new treatment targets within the peripheral or central trigeminovascular systems, or both, and the cranial parasympathetic system will be essential to expanding the disease-specific treatment options available to patients. Additionally, identifying key mechanistic pathways and targets within rostral brainstem and supratentorial brain regions that modulate nociceptive and other networks that generate migraine symptoms will be essential for modifying the expression of the disease. Similarly, expanding and validating the genes and their products that are associated with migraine, and understanding the molecular mechanisms by which they lead to expression of the disease, could identify genetic endophenotypes (subgroups), which should facilitate drug development and an individualised approach to treatment and disease modification. Finally, the influence of aggressive migraine prevention on disease course, serious adverse outcomes (eg, ischaemic stroke), and the occurrence of comorbid diseases (eg, depression, epilepsy) should be the focus of prospective, longitudinal disease-outcome registries.

Declaration of interests

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